State-Dependent Cognitive Processing in Health and Disease: Linking Resting State and Task Regulation in ADHD

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von
Anthony Schläpfer
von
Davos

Promotionskommission
Prof. Dr. sc. nat. **Lutz Jäncke** (Vorsitz)
Prof. Dr. sc. nat. **Daniel Brandeis** (Leitung der Dissertation)
Prof. Dr. sc. nat. Peter Achermann
Prof. Dr. sc. nat. Thomas König

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Anthony Schläpfer

„Gehirn: ein Organ, mit dem wir denken, daß wir denken.“

Ambrose Bierce

Contents

Summary

Cognitive dysfunction is a core problem in psychiatric disorders such as ADHD (Attention-deficit/hyperactivity disorder), one of the most frequent psychiatric disorders in children and adolescents. The brain mechanisms underlying disorders such as ADHD are still one of the major unresolved mysteries of science. Several scientific fields such as psychology, medicine, biology, chemistry, physics or even mathematics try to understand the complexity of the brain states supporting cognitive function. A major aspect of the brain complexity is its plasticity and dynamical adaptions in ever changing environments leading to interactions of different cognitive states.

In this thesis, I focused on two cognitive states, the resting state and the task state. In the resting state, unlike sleeping, the person is awake, conscious and ready to respond as soon as a cognitive demand increases. The task state is characterized by a cognitive state, in which stimuli need to be processed in a task specific way on a higher cognitive level. Failures of brain networks to adapt to cognitive states seem to have an important impact on psychiatric disorders such as ADHD. Neuroimaging uses tools such as functional magnetic resonance imaging (fMRI) or Electroencephalography (EEG) to describe brain function during such cognitive states.

The aim of this dissertation was to investigate how brain functions at rest and during cognitive tasks are influenced by these different states,

and how such state dependent processing differs in health and disease. We used simultaneous EEG-fMRI measurements in both states to describe temporal aspects of inhibition in healthy adults and state-dependent processing in children with ADHD.

In the first study, we aimed to clarify temporal and spatial activation patterns of common and task-specific brain mechanisms related to response inhibition. Our results identified a common inhibition network across tasks within the right IFG (inferior frontal gyrus). Using the temporal resolution of the EEG, we showed that ERP (event related potential) latency differences of the Stop P300 across subgroups of individuals correspond to different fMRI activations in the ACC (anterior cingulate cortex) and the left IFG. Hence, the inhibition process is not just reflecting several different processes supporting brain functions such as attention, working memory and response selection but the timing and interaction of these different processes is critical resulting in an interplay of neuronal processes and timing.

In a second study, we aimed to determine how resting state patterns are modified by task-evoked activations and how these modifications influence the behavior in children with ADHD. The transition or switch from rest to a task state seems to be altered in ADHD. Especially, the functional interaction between two prominent networks of these cognitive states (DMN: default mode network and CCN: cognitive control network) plays an important role in ADHD.

During resting state, FNC (functional network connectivity) showed significant group differences (children with ADHD vs healthy control group) between anterior and posterior parts of the DMN and regions related to the SMN (somato-motor network). In the task state, FNC only revealed significant group differences in long-range connections of the posterior part of the DMN and the CCN. Taken together, failures of brain networks across cognitive states seem to have an important impact on psychiatric disorders such as ADHD. This study highlights the importance of functional connectivity across different cognitive states illustrating that the link between different states seems to require an adaption of different networks.

This dissertation project contains two studies using simultaneous EEG-fMRI measurements to investigate how the individual timing can influence the cognitive state and how altered function of brain networks in each of the cognitive states could characterize psychiatric disorders such as ADHD. First, we could show that the timing of task states and the transitions between the processes is highly variable in inhibition tasks. This leads to the conclusion that inhibitory control in human behavior is dependent on a complex interplay of neuronal processes and timing, which may determine individual differences in brain mechanisms and goal-directed behaviors. Second, we found supporting evidence that state-dependent FNC disruption between the DMN and task-positive networks is a central feature in ADHD. Such malfunctions in a cognitive network of one state could have major consequenc-

es for another state and may reflect a pathophysiology of neuropsychiatric disorders.

Taken together, cognition and its underlying mechanisms are dependent on a timely synchronized interaction of several functional networks across different cognitive (vigilance) states. Minor inconsistencies in this complex system might characterize neuropsychiatric disorders.

Zusammenfassung

Kognitive Fehlfunktionen spielen eine zentrale Rolle bei psychiatrischen Erkrankungen wie ADHS (Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung), eine der häufigsten Störungen in der Kinder- und Jugendpsychiatrie. Die grundlegenden Mechanismen von ADHS sind noch immer nicht gut verstanden. Verschiedene Felder der Wissenschaft wie die Psychologie, Medizin, Biologie, Physik oder Mathematik versuchen mit verschiedenen Ansätzen die Komplexität des Gehirns zu erklären, um psychiatrischen Erkrankungen wie ADHS zu verstehen. Die plastischen und dynamischen Eigenschaften des Gehirns, welche für die täglichen Anpassungen an die stetig wechselnde Umwelt benötigt werden, sind zum grossen Teil verantwortlich für diese Komplexität. Das Gehirn besteht aus kognitiven Zuständen oder Netzwerken, welche sich jeweils an die entsprechende Situation oder die Umwelt anpassen.

Die vorliegende Arbeit untersuchte die verschiedenen kognitiven Zustände wie der Ruhezustand und der Aufgabenzustand bei Probanden mit ADHS sowie auch bei gesunden Probanden. Im Ruhezustand ist die Person wach, bewusst und allzeit bereit, auf eine kognitive Aktivität (z.B. eine mathematische Aufgabe zu lösen) zu reagieren. Der Aufgabenzustand ist charakterisiert durch einen höheren kognitiven Zustand, in welchem externe Stimuli verarbeitet werden müssen (z.B.

Kopfrechnen, um eine mathematische Aufgabe zu lösen). Fehler in diesen Zuständen oder Netzwerken scheinen eine wichtige Rolle bei psychiatrischen Erkrankungen wie ADHS zu spielen. Neuronale Messmethoden wie funktionelle Magnetresonanztomographie (fMRT) oder Elektroenzephalographie (EEG) versuchen, mittels Bildgebung solche kognitiven Zustände oder Netzwerke darzustellen, um die zu Grunde liegenden Prozesse zu beschreiben.
Das Ziel dieser Arbeit war es, die Prozesse im Gehirn, welche verantwortlich sind für die Interaktion von zwei verschiedenen kognitive Zuständen (Ruhezustand und Aufgabenzustand) zu erforschen. Des Weiteren wollten wir zeigen, wie sich diese Interaktion bei Probanden mit ADHS und gesunden Kontrollprobanden unterscheidet. Dazu nutzten wir simultane EEG-fMRT Messungen im Ruhe- und Aufgabenzustand bei gesunden Erwachsenen und Kindern mit und ohne ADHS.

In der ersten Studie untersuchten wir die temporalen und räumlichen Aktivitäten von gemeinsamen und aufgabenspezifischen Gehirnprozessen während zweier Inhibitionsaufgaben (Hemmungsaufgaben). Die Resultate zeigten ein gemeinsames Inhibitionsnetzwerk bei beiden Aufgaben im rechten IFG (inferior frontal gyrus). Mit der zeitlichen Auflösung des EEGs konnten wir zeigen, dass die individuellen ERP (event-related potential) Latenzen der P300 mit verschiedenen fMRT Aktivierungen im ACC (anterior cingulate cortex) und linken IFG korrelierten. Daraus schliessen wir, dass der Inhibitionsprozess nicht nur abhängig ist von unterschiedlichen kognitiven Prozessen wie Auf-

merksamkeit, dem Arbeitsgedächtnis oder der Antworthemmung, sondern auch das Timing und die Interaktion der oben genannten Prozesse eine wichtige Rolle spielen.

In der zweiten Studie ermittelten wir bei Kindern mit und ohne ADHS wie sich der Ruhe- und Aufgabenzustand gegenseitig beeinflussen und modifizieren können. Wir untersuchten die Auswirkungen dieser Modifikationen auf das Verhalten von Kindern mit ADHS. Der Übergang oder Wechsel vom Ruhezustand zum Aufgabenzustand scheint eine wichtige Rolle bei ADHS zu spielen. Speziell die Interaktion oder Verbindung zwischen zwei prominenten und gut untersuchten Netzwerken (DMN: default mode network und CCN: cognitive control network) haben einen wichtigen Einfluss auf ADHS. Unsere Resultate zeigten im Ruhezustand signifikante Gruppenunterschiede (zwischen Kinder mit ADHS und einer Kontrollgruppe) zwischen Verbindungen im anterioren und posteriorne Bereich des DMNs und Verbindungen im SMN (somato-motor network). Im Aufgabenzustand fanden wir signifikante Gruppenunterschiede zwischen weitreichenden Verbindungen im posterioren Bereich des DMNs und Verbindungen im CCN. Zusammengefasst kann man sagen, dass Fehlfunktionen in Gehirnnetzwerken bei verschiedenen Zuständen (hier Ruhezustand und Aufgabenzustand) einen Einfluss auf psychiatrische Erkrankungen wie ADHS haben können. Diese Studie bestätigt die Wichtigkeit von funktionellen Verbindungen und deren Modifikationen in verschiedenen kognitiven Zuständen bei psychiatrischen Erkrankungen.

In der vorliegenden Arbeit versuchten wir, mit Hilfe von simultanen EEG-fMRT Messungen den Einfluss vom individuellen (neuronalen) Timing auf kognitive Zuständen zu erläutern sowie zu klären, wie Fehlfunktionen in diesen Zuständen zu psychiatrischen Erkrankungen wie ADHS führen können. Erstens zeigten wir, wie das Timing in einer Arbeitsaufgabe (Hemmungsaufgabe) einen kritischen Faktor sein kann. Dies führt zu der Annahme, dass das menschliche Verhalten davon abhängt ist, wie neuronale Prozesse und das Timing dieser Prozesse zusammenspielen, um individuelles zielgerichtetes Verhalten zu erzielen. Zweitens konnten unsere Resultate zeigen, dass Fehlfunktonen in neuronalen Verbindungen zwischen dem DMN und CCN in zwei kognitiven Zuständen (Ruhezustand und Aufgabenzustand) eine zentrale Rolle spielen bei Kindern mit ADHS. Fehlfunktionen in einem Zustand können einen anderen (z.B. Aufgabenzustand) beeinflussen und schliesslich zu einer neuropsychiatrischen Erkrankung führen.

Als Schlussfolgerung kann man sagen, dass die Kognition und deren zugrundliegenden neuronalen Prozesse abhängig sind von zeitlich genau abgestimmten Verbindungen von neuronalen Netzwerken in verschiedenen Zuständen. Schon kleine Abweichungen vom Timing oder Veränderungen funktionaler Verbindungen können das komplexe Systems des Gehirns signifikant beeinflussen und zu neuropsychiatrischen Erkrankung führen.

List of Abbreviations

ACC	Anterior cingulate cortex
ADHD	Attention deficit hyperactivity disorder
BCG	Ballistocardiogram
BOLD	Blood-oxygen-level-dependent
CBCL	Child behavior checklist
CCN	Cognitive control network
DLPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
DSM-5	Diagnostic and statistical manual of mental disorders
EC	Eyes closed
ECG	Electrocardiogram
EEG	Electroencephalography
EO	Eyes open
EPI	Echo planar imaging
ERP	Event-related potential
FEF	Frontal eye fields
fMRI	Functional magnetic resonance imaging
FNC	Functional network connectivity
IC	Independent component
ICA	Independent component analysis
IFG	Inferior frontal gyrus

IPL	Inferior parietal lobule
PCA	Principal component analysis
PCC	Posterior cingulate cortex
PET	Positron-emission tomography
PFC	Prefrontal cortex
PMC	Premotor cortex
RSN	Resting state network
SM	Spatial component maps
SMA	Supplementary motor area
SMN	Somatomotor network
SSRT	Stop-signal reaction time
TC	Time course
TMS	Transcranial magnetic stimulation

1 General Introduction

1.1 State-dependent cognitive processing

Cognition and its underlying mechanisms along with its dysfunction are still one of the major unresolved mysteries of science. Several scientific fields such as psychology, medicine, biology, chemistry, physics or even mathematics try to understand the complexity of the brain. In particular, the scientific approach to understand the brain's function as a highly dynamic system with multiple levels, where cortical regions, cell assemblies or even single neurons interact with each other, has only recently begun.

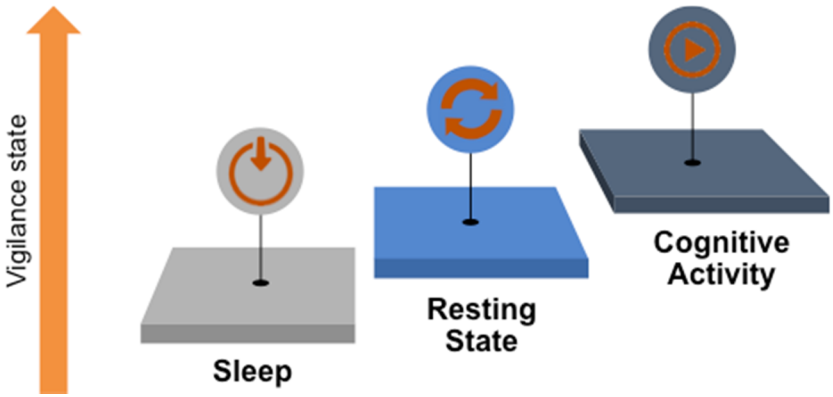
A major aspect of the brain complexity is its plasticity and its ability for dynamic adaptions in ever changing environments. The so called Ashby's "law of requisite variety" (Ashby, 1958) states that a systems response must be matching to diverse environmental disturbance to maintain internal stability. The brain as a system seems to operate in a similar manner. It has to maintain the internal stability by processing highly variable external stimuli such as sensory inputs. This dynamic system gives rise to different mental states, which are thought to correspond to different networks arising through transient binding of widely distributed cell assemblies according to a theory of brain networks (Varela, 1995). Francesco Varela already described in 1995 that cognitive states such as perception, memory or motivation are the matter of

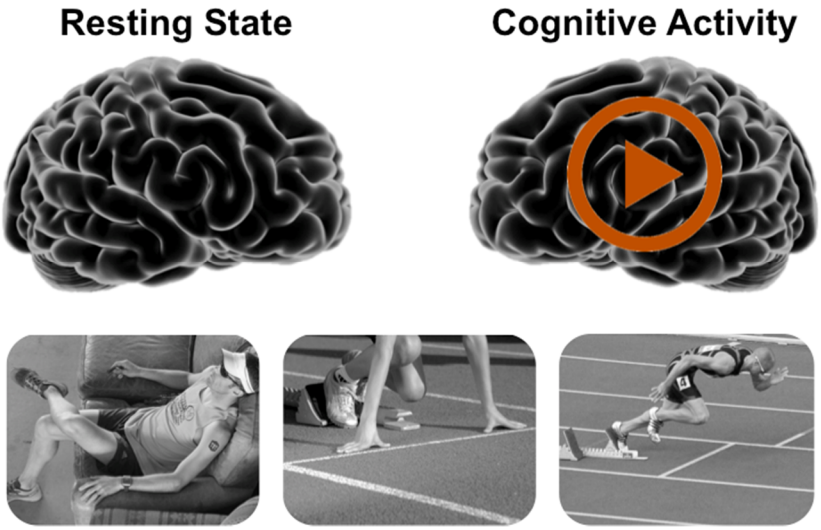
coordination of many different brain regions. In other words, the brain is able to self-organize its state based on external and internal stimuli while connecting brain region, cell assemblies or neurons to the specifics of the current situation. This dynamic self-organization is thought to lead to the highly complex mechanisms of cognition.

In this thesis, we focused on two cognitive states, the resting state and the task state. In the resting state, unlike sleeping, the person is awake, conscious and ready to respond as soon as a cognitive demand increases. The task state is characterized by a cognitive state, in which external stimuli need to be processed on a higher cognitive level. Neuroimaging uses tools such as functional magnetic resonance imaging (fMRI) or Electroencephalography (EEG) to describe such cognitive states. However, most of these studies focused just on a single state and did not investigate how the brain reorganizes its networks across different cognitive states.

Deco et al. (Deco et al., 2009) described that the resting state an task state could be linked and are used in a dynamic system. The resting state behaves like an "active standby" mode that is prepared and ready to "switch" to the task mode to adapt the changing environments. Interactions between the intrinsic neuronal activity of the resting state with task evoked extrinsic activity by cognitive processes can be extrapolated to a more complex system of higher cognitive function. The default mode network (DMN) is such a stable state during rest and plays an important role between resting and task state. Findings suggest that a defective transition of the DMN from a rest to a task state

leads to failures in attentional demands (Posner et al., 2014). Normal variations of the DMN during the transition of different cognitive states may interfere with task-relevant attentional networks that would be mirrored on the behavioral level by periodic and transitory performance deficits such as increase of reaction times and frequency of errors (Konrad et al., 2006). A dysfunction of the DMN have been reported in several mental disorders such as Attention-deficit/hyperactivity disorder (ADHD) (Castellanos et al., 2008; Fair et al., 2010; Sonuga-Barke and Castellanos, 2007a; Sun et al., 2012; Uddin et al., 2008) or dementia, schizophrenia, depression, anxiety, epilepsy and autism (Broyd et al., 2009). In the next two chapters, we will have a closer look at the two different cognitive states while discussing its impact on diseases such as ADHD.





1.2 Resting State

The resting brain is very interesting from the perspective of a dynamic system as it is organized of temporally correlated activities of spatially segregated brain structures called resting state networks (RSN). The discovery of resting state activity by Biswal and colleagues (Biswal et al., 1995) was quite by accident. Actually, while they were looking for activated brain regions during bilateral finger tapping, they also found activated brain areas for hand movement during rest. Furthermore, they corrected their data for heart rate and respiration to ensure that these slow fluctuations (<0.1Hz) are "real" brain activation and not an artifact. These findings were puzzling for current neuroimaging studies,

because those were on task-related neuronal activations detected by blood-oxygen-level-dependent (BOLD) contrasts (Ogawa et al., 1990) with fMRI. It was discussed that there was a need for a baseline of brain activity due to these findings (Gusnard and Raichle, 2001). Hence, Raichle and colleagues verified the results of Biswal et al. using positron-emission tomography (PET) during rest and considered this state as a default mode of brain activity (Raichle et al., 2001). Future studies performed such resting state analysis and provided the existence of the DMN as a RSN (Snyder and Raichle, 2012). The DMN is captured as initially reported by Raichle et al. (Raichle et al., 2001) along the anterior-posterior and inferior-superior axes (Buckner et al., 2008; Harrison et al., 2008) including the precuneus, the posterior cingulate cortex (PCC), the medial prefrontal cortex (MPFC) and the lateral, medial and inferior parietal cortex. The DMN shows higher activity in absence of a task when subjects are in a state of wakeful rest while their neural state is related to daydreaming, recovering, conceiving the perspective of others or mind-wandering (Buckner et al., 2008). Conversely, during a cognitive state with a goal-directed task the DMN becomes deactivated corresponding to increase attentional demands (Buckner et al., 2008; Raichle and Snyder, 2007). Its activity is attenuated but not absent during the transition from rest to a task state (Eichele et al., 2008; Greicius and Menon, 2004). Additional investigations into resting state and its dynamics revealed brain regions belonging to further RSN than the DMN and are comparable with systems involved in cognitive processes such as executive processing, inhibi-

tion, movement, vision, language and other sensory and cognitive processes (Damoiseaux et al., 2006; Fox et al., 2005). While these RSN show higher activation during task processing, the DMN exhibits the opposite pattern with increased activation during resting state and an attenuation in a cognitive task. The functional meaning of resting state and RSN is under continued discussion (Buckner and Vincent, 2007; Deco et al., 2009; Morcom and Fletcher, 2007; Raichle and Snyder, 2007; Zhang and Raichle, 2010). Some people described the resting state as noise or just non-neuronal components. An interesting fact, which supports the theory of a baseline neural activity, is the metabolic cost of resting state. The metabolic cost of neural activity during rest far exceeds that of activity evoked specifically by performing a task (Raichle and Mintun, 2006). Zhang and Raichle (Zhang and Raichle, 2010) described this issue very compelling by comparing the resting state with the dark energy: "*The driving force behind the apparent acceleration of the expansion of our universe is believed by many to be a previously unaccounted for 'dark energy', which constitutes approximately 75% of the total mass - energy in the cosmos. Like our cosmos, the brain also has its own 'dark energy'. Indeed, 'visible' elements of brain activity - neuronal responses to environmentally driven demands - account for less than 5% of the brain's energy budget, leaving the majority devoted to intrinsic neuronal signaling*". The large cost of its metabolic activity does not prove its functional role, but it constitutes its physiological importance.

In the last decade, several studies have reported altered resting state brain activity in diseases. Especially the study of pathophysiology of neuropsychiatric diseases such as ADHD is now investigated by resting state fMRI by looking at RSN (Castellanos and Proal, 2012; Fair et al., 2010; Konrad et al., 2006; Posner et al., 2014). It is suggested that such RSN deficits might contribute directly to inattention, impulsivity and other ADHD symptoms (Liston et al., 2011). Hence, measurement of resting state activity might help us to understand the physiology behind complex diseases that affect the human brain and might become a diagnostic tool for psychiatric diseases (Zhang and Raichle, 2010). Further insights about RSN alterations in ADHD and its underlying mechanisms will be discussed in chapter 1.4.

1.3 Task State

The task state is a set of cognitive states, which are driven by higher cognitive functions while processing the input of external stimuli. These stimuli coincide to task-specific rules and requirements, often involving critical timing, distinct processing stages and complex sets, as well as evaluations and expectancies. Similar to the resting state - that resembles a highly dynamic, multistate system – the task state contains dynamic time-dependent processes that are essential for higher cognitive performance (Bressler, 1995; Sporns, n.d.; 2011; Varela et al., 2001).

In this thesis, I want to focus on cognitive control, and particularly on response inhibition. Cognitive control and inhibition are prototypical executive functions that play an important role in controlling movements, impulsivity or goal directed behavior (Bari and Robbins, 2013; Diamond, 2013; Logan, 2015). The ability to inhibit or override a pre-programmed dominant motor response is crucial when unexpected situations occur, and compromised inhibitory control thus poses frequent disadvantages in daily life such as for flexible goal directed behavior in ever-changing environments (Verbruggen and Logan, 2008a). The suppression of actions that are inappropriate or no longer needed are required to preserve flexible behavior.

The inhibition of a motor response is related to several different neuronal processes such as attention, working memory and response selection (Chambers et al., 2009). A particularly important aspect of inhibition is the timing of the neural inhibition process, which may be linked to regions and tasks but also individual differences in behavior, task strategies or psychopathology. The poor temporal resolution of fMRI makes it difficult to clarify timing-dependent brain regions of inhibition (Verbruggen et al., 2013). To disentangle the timing of response inhibition mechanisms, a method with higher temporal resolution like EEG is required. In the study A we used simultaneous EEG-fMRI recordings to disentangle temporal and spatial aspects of response inhibition to gain more detailed information about timing and spatial activa-

tion patterns of common and task-specific brain mechanisms related to response inhibition.

To date, much of our understanding of higher cognitive brain functions is related to task- or stimulus- based studies. These neuroimaging approaches overlooked the interactions between and within brain regions. Studies are needed to compare intrinsic connectivity during resting states and task-based networks driven by goal-directed behavior (Stevens, 2016). The multifunctional nature of the brain's network organization performs a dynamic network interaction between and within brain regions (McIntosh, 2000; Sporns, 2011). Sporns described cognition as collective property of complex interconnected neural elements. There is a shift in focus from regional brain activations to dynamic network organization. This shift to a dynamic network model also matches and is more comparable to the phenomenon of resting state activity as a multistate, dynamic system. This leads to a further interesting question regarding the link between resting state and task state networks. How different or similar are neural patterns of networks during a specific cognitive task and in the absence of stimulus input? How does the task demand modulate the functional network connectivity (FNC) of the DMN? We already described the properties of the DMN and its opposing activity in both states. Furthermore, the DMN shows a prominent interaction with a network, the cognitive control network (CCN) or task positive network, which encompasses the dorsal anterior cingulate cortex or supplementary motor area (SMA),

dorsolateral prefrontal cortex (DLPFC), inferior frontal junction, anterior insular cortex and posterior parietal cortex and is involved in executive cognitive processes such as working memory and inhibitory control (Cole and Schneider, 2007). However, the CCN shows more activation during tasks and its regions appear to be associated with increased alertness, response preparation or selective attention (Fox et al., 2005; Sonuga-Barke and Castellanos, 2007b). The DMN and CCN show anti-correlated behavior in relation to different task states. There is increasing evidence that the DMN deactivation which is the basis of the anti-correlated architecture is functionally relevant for cognitive performance (Anticevic et al., 2012). The DMN activation is attenuated and the CCN activation increases as attentional demands increase, whereas during a phase of "rest" the anti-correlation remains, namely the DMN activation is increased and the CCN activation is reduced (Fox et al., 2005; Grady et al., 2010; Raichle et al., 2001). However, the DMN activity is not completely abolished during task performance, which suggests that the DMN seems to modulate task relevant functional networks.

Recent neuroscientific studies try to understand the interaction or cooperation of the different cognitive states like resting and task states. It is an important issue to investigate how resting state patterns modify a cognitive state or are modified by task-evoked activation and how these modifications influence the behavior. Recent studies suggest that resting state is like a "prior" for cognitive task states (Fox et al., 2006; He et al., 2007) and its connectivity constrains subsequent activity of a

cognitive task state, as well as maintains predictions about forthcoming stimuli (Spadone et al., 2015). Another hypothesis of these two states considers the resting state as a default state that must be re-organized for cognitive tasks (Biswal et al., 1995).

Taken together, the interaction of the resting state and task state network could be described as a highly complex system. Failures of complex systems might be spectacle to have negative outcomes. Hence, it is not surprising that alteration of FNC in the human brain could be responsible for various brain disorders. In the next chapter, we want to discuss such alteration of FNC in ADHD.

1.4 ADHD alterations across cognitive states

Attention-deficit/hyperactivity disorder (ADHD) is one of the most frequent psychiatric disorders in school age children with a prevalence of around 5% (Polanczyk et al., 2007) and the susceptibility of ADHD is highly hereditary (Faraone et al., 2005). The cardinal symptoms of ADHD are described by inattenation, hyperactivity and impulsivity ("Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)," 2013). The DSM defines three subtypes of ADHD based on the single and combined symptoms of inattention, hyperactivity and impulsivity. The range and combination of these symptoms of this complex neurodevelopmental disorder probably forms a heterogeneous group of different clinical phenotypes.

Neuroimaging could give important insight on the neural mechanism

of ADHD. Studies in ADHD focused on a few isolated regions. Evidence showed that ADHD reflect dysfunctions in specific regions that subserve cognitive, motor and attentional functions (Bush, 2009). To date, much of our understanding of brain functions in ADHD is related to task- or stimulus- based studies. These neuroimaging approaches overlooked the interactions between and within brain regions in ADHD. Recent models shift its focus from regional brain abnormalities to dysfunction in network organization. Posner et al. (Posner et al., 2013) showed that children with ADHD have deviations in two different neural systems including executive attention and emotional regulation, which emphasizes the importance to explore multiple neural networks.

Most of these studies used resting state to compare such functional network organizations. An advantage of resting state fMRI compared to task-based fMRI is the reliable detection of resting state networks across subjects and sessions (Biswal et al., 2010). Several atypical integrity of FNC has been found. The most prominent network and its association with ADHD is the DMN (Castellanos et al., 2008; Fair et al., 2010; Sun et al., 2012; Uddin et al., 2008). It is suggested that ADHD could be considered a DMN disorder (Sonuga-Barke and Castellanos, 2007b). The transition from rest to a task state and the deactivation or suppression of the DMN is associated with momentary lapses in attention (Weissman et al., 2006). These findings suggest that a defective transition of the DMN during rest and task state lead to failures in attentional demands (Posner et al., 2014). Misconfigurations of the

DMN during the transition of different cognitive states may interfere with task-relevant attentional networks that would be mirrored on the behavioral level by periodic and by transitory performance deficits such as increase of reaction times and frequency of errors (Konrad et al., 2006). In contrast, the task positive network CCN shows more activation during tasks and its regions appear to be associated with increased alertness, response preparation or selective attention (Fox et al., 2005; Sonuga-Barke and Castellanos, 2007b). Anterior regions of the CCN which have a critical role in attention, executive processing, response selection, error detection or response inhibition have been suggested to influence behavioral inhibition in children with ADHD (Bush, 2009). The DMN activation is attenuated and the CCN activation increases as attentional demands increase, whereas during a phase of "rest" the anti-correlation remains, namely the DMN activation is increased and the CCN activation is reduced (Fox et al., 2005; Grady et al., 2010; Raichle et al., 2001). Castellanos and colleagues (Castellanos et al., 2008) found exactly this anti-correlation between central regions of the DMN (precuneus, PCC) and regions of the CCN such as the dorsal anterior cingulate cortex (dACC), the right inferior frontal gyrus (rIFG) and the right medial frontal gyrus in adults with ADHD and healthy control participants. However, the extent of the anti-correlation between the DMN and CCN was weaker in their ADHD group compared to the healthy controls, and especially long-range connections between the dACC and the precuneus/PCC were affected (Castellanos et al., 2008). Several studies including children, adolescents or adults

with ADHD found similar supporting results that the anti-correlation between the DMN and the CCN is reduced or attenuated during both resting state (Castellanos et al., 2008; Sun et al., 2012) and task state (Fassbender et al., 2009; E. B. Liddle et al., 2011).

Taken together, failures of brain networks to adapt cognitive states seem to have an important impact on psychiatric disorders such as ADHD. State specific deviations in the long-range connection between the anterior and poster part of the DMN or variances across states like the anti-correlation between the DMN and CCN might describe the neuronal complexity of ADHD. The link between different states requires an adaption of different networks. These dynamic modulations are driven by external and internal stimuli and will become of increasing importance in clinical and translational medicine (Sporns, 2011).

1.5 Methods to study cognitive states

One-way to investigate how the brain functions is to focus on the brain's response to external stimuli. However, this framework treats the brain as an input-output system and ignores its dynamic aspect. Two important factors of a dynamic system are time and connectivity. Both factors can be observed and recorded with neuroimaging techniques such as EEG or fMRI. The advantage of EEG compared to fMRI is its high temporal resolution and its direct relation to electric neuronal activity (Pascual-Marqui et al., 2011), whereas the advantage of the fMRI is its high spatial resolution compared to EEG. While both

techniques differ in their temporal and spatial resolution, they reveal functional networks that show a number of consistent topological features (Sporns, 2011). Task state fMRI studies often apply a subtraction method to identify specific brain regions that are attributed to different stimuli in a cognitive task. This will mostly lead to specific activations in task-related brain regions with high spatial resolution, whereas the EEG data could be dissected into stimulus linked event-related potentials (ERP) with a high temporal resolution. To maximize the advantages both techniques it is very useful to collect data with a simultaneous EEG-fMRI approach. Networks of functional connectivity in the resting or task state using the BOLD response could be characterized by several methods. We want to examine briefly the methods of independent component analysis (ICA) that we applied here. ICA is a model-free approach and does not require any a priori predictions. In general, ICA decomposes the data into maximally independent components based on their temporal or spatial structure (McKeown et al., 1998). The independent components (IC) are associated with a time course that could be used to calculate FNC (Jafri et al., 2008) as pairwise correlation of the average connectivity during the scan durations.

1.6 General aims and hypotheses

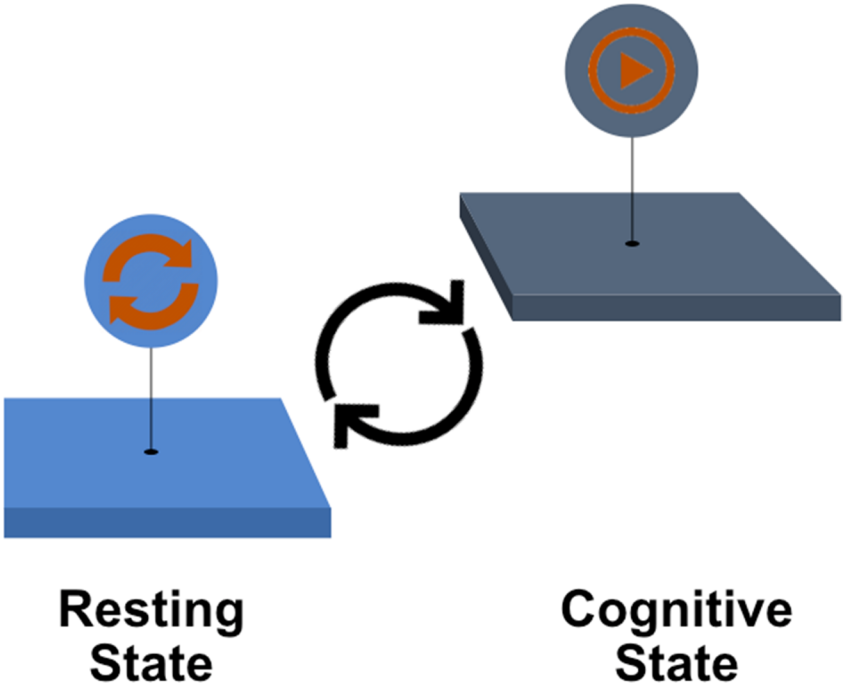
The aim of this dissertation was to investigate how brain functions at rest and during cognitive tasks are influenced by these different states, and how such state dependent processing differs in health and disease.

We used simultaneous EEG-fMRI measurements in resting and task states to describe temporal aspects of inhibition in healthy adults and state-dependent processing in children with ADHD.

In the first study, we aimed to clarify temporal and spatial activation patterns of common and task-specific brain mechanisms related to response inhibition. Individual differences in timing and latency distribution have received less attention. Using the strength of both modalities (EEG and fMRI) we investigated the temporal and spatial differences in more detail to reveal subgroups of individuals with distinct timing differences. We particularly searched for clusters of individuals showing distinct timing characteristics and furthermore distinct activation clusters of response inhibition between and within the tasks.

In a second study, we aimed to determine how resting state patterns modify a cognitive state or are modified by task-evoked activations and how these modifications influence the behavior in children with ADHD. Resting and task states seem to have an important aspect in ADHD. Between DMN and CCN (anti-correlation) and within DMN, functional connectivity seems to play an important role in ADHD. A common feature resulted in a disorganized DMN dynamics that cannot be effectively suppressed when switching to another cognitive state (Aboitiz et al., 2014). We hypothesized that in both states, children with ADHD show impaired FNC between components of the DMN and CCN in the form of an attenuated anti-correlation between the

networks in children with ADHD. Furthermore, we expected correlations between the anti-correlation and clinical ADHD scores.



2 Study A:

Individual timing differences reveal distinct spatial inhibition patterns across response inhibition tasks: A simultaneous EEG-fMRI study

Anthony Schläpfer[1,2], Katya Rubia[3], Silvia Brem[1,2], Daniel Brandeis[1,2,4,5] *

[1] Department of Child and Adolescent Psychiatry and Psychotherapy, Psychiatric Hospital, University of Zürich
[2] Neuroscience Center Zurich, University of Zurich and ETH Zurich, Zürich, Switzerland
[3] Department of Child and Adolescent Psychiatry, King's College London, De Crespigny Park, London, UK
[4] Zurich Center for Integrative Human Physiology (ZIHP), University of Zurich, Zürich, Switzerland
[5] Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim/Heidelberg University, 68159 Mannheim, Germany

2.1 Abstract

Response inhibition refers to the suppression of actions that are inappropriate or no longer needed for a flexible goal directed behavior in ever-changing environments. Despite extensive research on clinically impaired response inhibition, limited work has addressed individual neural differences in unimpaired response inhibition. Here we used simultaneous EEG-fMRI in two response inhibition tasks to gain more detailed information about timing and spatial activation pattern of common and task-specific brain mechanisms related to response inhibition. 22 (12 female, 10 male) healthy, right-handed participants performed two response inhibition tasks (Stop-Signal and NoGo-Flanker) during one single session. Our results identified a common inhibition network across tasks and clarified the temporal aspects of response inhibition. We showed that the right and left inferior frontal gyrus (IFG) as well as the left dorsolateral prefrontal cortex (DLPFC) play an important role in the frontal network of response inhibition. Importantly, the temporal resolution of the EEG enabled us to define subgroups that are only correlated within the Stop-Signal reaction time (SSRT). Latency differences of subjects' Stop P300 event-related potentials (ERP) were found to correspond to different fMRI activation in the anterior cingulate cortex and the left IFG. These findings based on EEG informed fMRI thus proved to be useful for interpreting (sub)group differences in timing of response inhibition. Future work should consider whether such variability in neurophysiological timing of inhibition underlies inhibitory deficits in clinical groups, and how

such variability can account for interindividual differences in psychiatric diseases.

2.2 Introduction

Cognitive control including inhibition are executive functions that play an important role in controlling movements and impulsivity (Bari and Robbins, 2013; Diamond, 2013; Logan, 2015). The ability to inhibit or override a preprogrammed dominant motor response is crucial when unexpected situations occur, and compromised inhibitory control thus poses frequent disadvantages in daily life such as for flexible goal directed behavior in ever-changing environments (Verbruggen and Logan, 2008a). The suppression of actions that are inappropriate or no longer needed is required to preserve flexible behavior. These adjustments of adapting subjects' behavior to a dynamic environment are influenced by individual goals and strategies and thus individual differences regarding response inhibition may be expected for reactive control to unpredictable situations (Jahfari et al., 2012). Importantly, problems of inhibition and impulsivity characterize several neurological and psychiatric disorders such as attention deficit hyperactivity disorder (ADHD), schizophrenia or obsessive-compulsive disorders (Aron et al., 2003; Brandeis et al., 1998; Hughes et al., 2012; Lei et al., 2012; Rubia et al., 1999).

The inhibition of a motor response is related to several different neuronal processes such as attention, working memory and response selection (Chambers et al., 2009). Each of these processes evokes distributed activations including frontal lobe (inferior frontal gyrus and pre supplementary motor area), subthalamic nucleus, basal ganglia and

parietal cortex (e.g. (Chambers et al., 2009; Goghari and MacDonald, 2009; Mostofsky and Simmonds, 2008; Simmonds et al., 2008).

Two very common and well-studied inhibitory control tests are Go/NoGo and Stop tasks. Both measure the ability to withhold a dominant response (Go). In the Go/NoGo task a motor response (Go) has to be either executed or inhibited depending on whether a Go stimulus which is more frequent or a NoGo stimulus (typically less than 30% of trials) are presented. In the Stop task an already triggered and possibly initiated response to a pre-potent Go stimulus needs to be inhibited after a Stop signal follows unexpectedly the Go signal after a few hundreds of milliseconds. Thus the Go/NoGo task has a higher load on response selection and selective attention as the differential stimuli (Go or NoGo) indicate a different response. The stop task instead has a higher load on response inhibition, as the Go response that is already triggered by the Go stimulus and may be on its way of execution has to be withheld (Rubia et al., 2001). So far, response inhibition studies in healthy subjects focused on task differences and associated regions on the group level. However, less work has addressed individual differences in unimpaired response inhibition. Some studies focused on task performance, reaction time (Chao et al., 2009; Forstmann et al., 2008), behaviors like impulsivity (Horn et al., 2003; Shen et al., 2014) or motivation (Greenhouse et al., 2013; Leotti and Wager, 2010). A review of error processing in Go/Nogo tasks (Hester et al., 2004) showed individual differences in both demographic and performance measures.

Additionally, individual differences play an important role for subgroup classification in heterogeneous disorders such as ADHD (Nigg et al., 2005; Sonuga-Barke, 2002).

A particularly important and not well-studied aspect of inhibition is the timing of the neural inhibition process, which may be linked to regions and tasks but also individual differences in behavior, task strategies or psychopathology. Timing of the stop process measured by the Stop-Signal reaction time (SSRT) is the main behavioral variable in the Stop-Signal task (Logan and Cowan, 1984) because it has been related to neural mechanisms of response inhibition (Cohen et al., 2010). Even though it is assumed that the Stop-Signal task is robust against individual strategic adjustments (Boehler et al., 2012), Leotti and Wager (Leotti and Wager, 2010) showed that motivational differences between groups or subjects can distort the SSRT resulting in different strategies of performance. Based on neural mechanisms, individual differences of the SSRT showed correlations with the inhibitory motor areas (superior and precentral frontal cortices) (Li et al., 2006) or the right inferior frontal gyrus (IFG) (Hughes et al., 2012). Furthermore, a recent electroencephalographic (EEG) study (Wessel and Aron, 2015) showed that the inhibition P300 (Stop P300, NoGo P300) is highly correlated with the SSRT. Additionally, brain stimulation methods such as transcranial magnetic stimulation (TMS) showed that right inferior frontal gyrus (IFG) and supplementary motor areas (SMA) specifically modulate SSRT (Chambers et al., 2009).

A fMRI meta-analysis (Swick et al., 2011) suggested that different

inhibition tasks (Go/NoGo and Stop-Signals tasks) evoke both common and task-specific activations in several brain regions that are involved in the neuronal mechanisms of response inhibition. Despite differences in procedure and stimuli, the basic concept of inhibitory response control is highly similar and hence it is assumed to activate the same neuronal mechanisms of inhibition (Huster et al., 2013). Such response inhibition tasks activate frontal regions such as inferior, middle and superior frontal gyrus, the insula, dorsolateral prefrontal cortex (PFC), anterior cingulate cortex (ACC), as well as regions in the (pre-) SMA. Additional regions in the striatum, inferior parietal cortex and the precuneus seem to play an important role in the network of response inhibition. The main difference in the two tasks is the timing of presentation of the Stop or NoGo cue relative to the stimulus. Three papers compared activation in the same subjects performing the two different tasks types: Rubia et al. (Rubia et al., 2001) found overlapping activations in lateral PFC, medial PFC and parietal lobes. Zheng et al (Zheng et al., 2008) found that the middle frontal gyrus is critical for response inhibition in both tasks and McNab et al. (McNab et al., 2008) found common activations in right inferior and middle frontal gyri, the left and right insula consistent with the meta-analysis of Swick et al. (Swick et al., 2011). However, the regions corresponding to response inhibition are known, but their specific function related to the inhibitory process itself are still not fully understood (Sharp and Bonnelle, 2010). Aron and colleagues (Aron, 2011) suggest that the

right inferior frontal junction implements attentional detection, whereas the more ventral sector of the right IFG implements inhibitory control. This is highly consistent with other studies suggesting the right IFG is the core region in the inhibition system (Aron et al., 2014; Rubia et al., 2003; Sebastian et al., 2015; Swick et al., 2011) converging with the finding that people with frontal lobe lesions in the right IFG are impaired on inhibitory control tasks (Goghari and MacDonald, 2009). Other studies emphasized the role of the pre-SMA (Chao et al., 2009; Sharp and Bonnelle, 2010). A recent review (Criaud and Boulinguez, 2013) suggests that some regions in the right lateralized parieto-frontal network and the pre-SMA may reflect different task settings or cognitive processes other than inhibition. Besides the role of the right IFG in response inhibition it is also suggested to be recruited when important cues are detected, no matter if an inhibition or go stimulus appeared (Hampshire et al., 2010; Sharp and Bonnelle, 2010). Rubia and colleagues (Rubia et al., 2003) assigned the brain activation of the right IFG with successful inhibitory control and the mesial frontopolar and bilateral inferior parietal cortices with inhibition failure or error detection. Aron and Poldrack (Aron and Poldrack, 2006) propose a network model of response inhibition including the right IFG, subthalamic nucleus and the pre-SMA. It is probably the interaction of regions such as IFG and pre-SMA and its underlying connectivity that is responsible for response inhibition (Sharp and Bonnelle, 2010). Furthermore, Verbruggen and Logan (Verbruggen and Logan, 2008b) indicate the importance of the timing during response inhibition in

brain regions surrounding the pre-SMA.

However, the variability in the activation patterns of fMRI findings may be related to individual differences. Key functions in disentangling the process of response inhibition could be the timing of brain functions or individual differences in behavior, task strategies or psychopathology. The poor temporal resolution of fMRI makes it difficult to determine the specific role of the pre-SMA and IFG (Verbruggen et al., 2013). To clarify the timing of response inhibition mechanisms a method with higher temporal resolution like Electroencephalography (EEG) is required.

The advantage of EEG compared to fMRI is its high temporal resolution and its direct relation to electric neuronal activity (Pascual-Marqui et al., 2011). Response inhibition evokes two event-related potential (ERP) components in the EEG: a frontal-centrally negative N200 and centrally positive NoGo P300 (De Jong et al., 1990; Simson et al., 1977). The NoGo P300 appears more directly linked to response inhibition than the N200 (Bekker et al., 2004; Bruin et al., 2001; Donkers and van Boxtel, 2004; Enriquez-Geppert et al., 2010) and the positive peak of the P300 at 200-600 ms after an inhibition signal (NoGo or Stop) is a common finding across response inhibitions tasks. These electrophysiological responses due to inhibition are interpreted as the same mechanisms irrespective of the precise tasks content (Huster et al., 2013), although just one study showed similar patterns of ERPs while comparing NoGo and Stop signals directly (van Boxtel et al.,

2001). EEG inverse modeling and simultaneous EEG-fMRI recordings suggest that sources underlying fronto-central ERPs are associated with the pre-SMA, tempoparietal regions, insula and the basal ganglia (Huster et al., 2011; Karch et al., 2008). However the association of the SMA and the P300 component was just found in simultaneous EEG-fMRI studies but not in inverse models suggesting (Huster et al., 2013) that the SMA is not directly linked to the EEG signal generation. Several studies focused on relating individual differences of response inhibition to scores such as impulsivity and attention (Dimoska and Johnstone, 2007; Shen et al., 2014), motivation (Greenhouse et al., 2013) or absentmindedness (Roche et al., 2005), i.e. measures of cognitive function and subclinical psychopathology. Interestingly, the inter-individual differences of ERP amplitudes could not be described by performance differences (Dimoska and Johnstone, 2007; Roche et al., 2005; Shen et al., 2014). However, these studies only looked for differences in amplitude of specific ERPs and did not consider variations in the timing.

Here we used simultaneous EEG-fMRI in the same subjects performing two non-randomized response inhibition tasks during the same session and thus avoided potential learning and mood effects. The aim of integrating both modalities in this study was gaining more detailed information about timing and spatial activation patterns of common and task-specific brain mechanisms related to response inhibition. Inhibition studies mostly used single tasks and relied on subtraction

methods to resolve response inhibition processes. We chose two widely used inhibition tasks involving both common and unique inhibitory processes, a tracking Stop-Signal task (Rubia et al., 2003) and a modified NoGo-Flanker task (Baumeister et al., 2014; Bunge et al., 2002; Iannaccone et al., 2015; Kopp et al., 1996; Meyer-Lindenberg et al., 2006). Both tasks measure the same cognitive construct of inhibiting a prepotent action (Swick et al., 2011), although inhibitory load is typically higher in the Stop-Signal task. EEG studies of response inhibition mostly looked at individual differences of amplitude or frequency. However, individual differences in timing and latency distribution have received less attention. Using the strength of both modalities (EEG and fMRI) we investigated the temporal and spatial differences in more detail to reveal subgroups of individuals with distinct EEG NoGo timing differences and furthermore fMRI activation distinctions that are neither caused by differences in task nor performance.

We hypothesized that both tasks show spatial activation overlap in the pre-SMA, ACC, the right IFG and parietal lobes, whereas the ERPs show a common NoGo P300 peaking between 200-600ms. We particularly searched for clusters of individuals showing distinct NoGo ERP timing characteristics and furthermore distinct activation clusters of response inhibition between and within the tasks.

2.3 Methods

2.3.1 Participants

22 (12 female, 10 male) healthy, right-handed adults with a mean age of 24.05 years (± 2.36 years, 21-29 years), no history of neurological or psychiatric disease and no contraindications for MRI scanning participated in the study. All participants completed a German version of the Conners' Adults ADHD Rating Scale (self-report and report by an observer) as this study was implemented in an ADHD study. The study was approved by the local ethics committee and met the guidelines of the declaration of Helsinki. Subjects received a voucher for their participation.

2.3.2 Tasks

Subjects obtained a detailed instruction about the two tasks with a short training session outside of the scanner. The two inhibition tasks were performed in a single EEG-fMRI session with the Stop-Signal task following the (easier) NoGo-Flanker task. There was a short break between the tasks of two minutes. Right before the tasks started, a short visual instruction was given to reduce any discrepancies.

2.3.2.1 Stop-Signal Task

A Stop-Signal task with an event-related design was used as described previously (Rubia et al., 2003) (Figure 1 A). There were 234 go trials and 60 no-go trials in total. Each trial consisted of a white arrow pointing right or left presented for 800 ms on a black background in the middle of the screen. The trials were followed by an average interstimulus interval of 1300 ms (jittered between 1100 and 1500 ms). Subjects had to press a left or right button with the index or middle finger, corresponding to the direction of the arrow (Go trials). In 20% of the trials the Go signals were followed pseudo randomly and unpredictably (about 250 ms later) by arrows pointing upwards (Stop signals). Subjects had to inhibit their motor responses on these trials. The initial interval between go and stop stimulus was 250 ms. A tracking algorithm continuously adapted this time interval to each subject's performance by recalculating the percentage of correct Stop trials after each Stop trial in order to reach about 50% successful and 50% failed Stop trials for each subject. The time interval between Go and Stop signal (stop-signal delay) increased by 50 ms when the subjects' overall inhibition was higher than 50%, making the task more difficult, or decreased by 50 ms when the percentage of inhibition was lower than 50%, making the task easier for the subject. The whole task lasted 9 min. Prior to scanning, written and oral instruction, followed by a short training consisting of 20 trials was given to the subjects. The stimuli

were presented using Presentation® software (Neurobehavioral Systems, Version 13.1.05.30.09).

NoGo-Flanker Task

A modified speeded Flanker task (Bunge et al., 2002; Iannaccone et al., 2015; Kopp et al., 1996) including an inhibition (NoGo) condition was used (Figure 1 B). Subjects had to focus on centrally presented targets (arrowheads or circles) while ignoring the distracting stimuli on both sides of the target (Flankers). They had to respond or withhold a response accordingly: left button-press if the arrowhead was pointing to the left side, right button-press when the arrowhead was pointing to the right side and no button-press when a circle was presented. The three experimental conditions included a congruent Go condition, when the flankers were compatible with the target (Go), an incongruent Go condition, when flankers and target (Go) were incompatible and a NoGo condition, when the target in the form of a circle surrounded by arrowhead flankers indicated to withhold the response (response inhibition).

The task was modified by an adaptive response window, which changed during the task according to individual subject's performance to achieve response errors for analysis. The task duration was approximately 10 minutes. The 180 experimental trials per run (60 trials per condition) were interspersed by 60 null trials and four breaks (9 s) where a centered fixation cross was presented. The stimuli were presented in a pseudorandomized design using Presentation® software (Neurobehavioral Systems, Version 13.1.05.30.09). Flankers were

displayed for 100ms followed by the actual target, which appeared for 150ms. The SOA of a trial summed up to 2360ms. Feedback on performance was given after blocks of 20 consecutive trials by displaying feedback pictures for 1000ms. Subjects were instructed to respond as quickly and accurately as possible. Prior to scanning, written and oral instruction, followed by a short training consisting of 20 trials was given to the subjects.

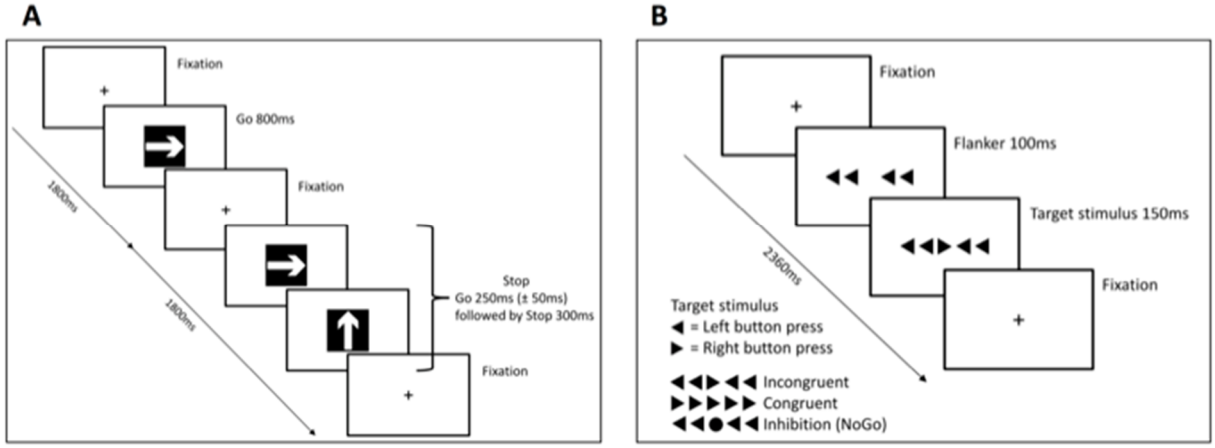


Figure 1: Trial timing and conditions of the Stop-Signal task (A) and the NoGo-Flanker task (B).

2.3.3 EEG acquisition and analyses

2.3.3.1 Recordings

Continuous EEG was recorded from 62 scalp and two electrocardiogram (ECG) electrodes with 5kHz and synchronized to the scanner clock and TR to minimize gradient residuals (Mandelkow et al., 2006), (filters highpass: 0.1Hz, lowpass for all scalp electrodes: 250Hz; for ECG channels: lowpass 1000Hz) simultaneously during fMRI-acquisition using MR-compatible equipment (BrainAmp DC-amplifiers by BrainProducts GmbH, Munich, Germany and EEG caps by EASYCAP GmbH, Herrsching, Germany). Electrode impedances were kept below 20 kΩ.

The recording reference was located at Fz, the ground electrode at AFz. The scalp electrodes covered the 10-20-system plus the following additional sites: FPz, AF1/2, FCz, CPz, POz, Oz, Iz, F5/6, FC1/2/3/4/5/6, FT7/8/9/10, C1/2/5/6, CP1/2/3/4/5/6, TP7/8/9/10, P5/6, PO1/2/9/10, OI1/2, LE/RE (left eye/right eye). O1'/2' and Fp1'/2' were placed more laterally to Oz/FPz (at 15% instead of the standard 10%) for more even coverage.

2.3.3.2 EEG Analyses

EEG data were processed using Analyzer 2.0.4 software (Brain-Products GmbH, Munich, Germany). MR-gradient and ballistocardio-

gram (BCG) artifacts were removed using sliding average template subtraction (P. J. Allen et al., 2000) and BCG correction was inspected manually. Data were subsequently down-sampled to 50ß0Hz and bandpass filtered from 0.1-49Hz with 50Hz notch. Ocular and residual BCG artifacts identified by their characteristic topography and time course (Debener et al., 2008; Jung et al., 2000) were removed using independent component analysis (ICA) (Jung et al., 2000). Amplitudes exceeding ±80µV (except ECG) were considered as artifacts and subsequently rejected from further analysis. After artifact removal, continuous EEG data was re-referenced to the average reference. To preserve pre-event topography and to avoid subsequent map distortion we did not do perform baseline subtraction (Brandeis et al., 1998).

The continuous EEG was segmented into stimulus-locked ERPs of 1500 ms (-500 ms to 1000 ms). The artifact free trials were averaged into NoGo/Stop and Go conditions for each participant. The grand mean was calculated using all subjects averaged trials for each task separate. We also calculated t-maps of component topographies for each task separately to clarify consistency of the inhibition P300 topographies (vs baseline). As supplementary analyses, we also report the results for the t-maps inhibition vs Go.

The P300 peak was calculated at the electrode Cz for each participant using a time window between 200 to 600 ms after stimulus onset, consistent with the typical time range of inhibition related P300 latencies. Based on the largest grand mean stop P300 activity which peaked at 300ms, we split the subjects based on their individual P300 peak detec-

tion results in the Stop task into two subgroups: The first group showed the P300 peak before 300 ms (fast: n=12) and the second group showed its P300 peak after 300 ms (slow: n=10). We also used the same subgroups to analyze the Flanker. Additional analyses based on an P300 latency median split, or a split between the first and the smaller second P300 yielded nearly identical groups and results.

2.3.4 fMRI acquisition and analyses

2.3.4.1 Recordings

MR images were acquired using a 3T Philips Achieva whole-body system (Philips Medical Systems, Best, the Netherlands) with a 32-elements receive head coil (Philips SENSE Head coil 32-elements) specifically designed for simultaneous recordings of EEG and fMRI. First we recorded phase and magnitude images at different echo times (TE_1 = 4.3 ms, TE_2 = 7.3 ms), which were used to generate a voxel displacement map. An echo planar imaging (EPI) sequence was applied for fMRI data recordings [TR: 1,960ms, TE: 30ms, 35 slices, 3 x 3 x 3mm voxel size, 0.7 mm slice gap, FA: 80°, FOV: 240 x 240 x 129mm]. Slices were aligned to AC-PC line. After acquisition of functional images, T1-weigthed images were recorded with a 3D MP-RAGE sequence [FOV: 270 x 254 x 176mm, sagittal orientation, 1 x 1 x 1 mm voxel size, TR: 6.9ms, TE: 3.2ms, flip angle: 9°].

2.3.4.2 fMRI Analyses

Preprocessing and analyses were conducted using SPM8 (Wellcome Trust Centre for NeuroImaging, UCL, London, UK). Images were realigned, unwarped using field maps to correct for motion artifacts, susceptibility artifacts and motion-by-susceptibility interactions (Andersson et al., 2001; Hutton, 2002) and slice time corrected. Next, T1-weighted anatomical images were segmented using the SPM8 procedure "New Segment" and the Forward Deformations obtained from the segmentation were applied to the anatomy and the realigned and co-registered EPI files. Finally, the data were smoothed with a Gaussian kernel of 6mm full-width at half maximum. The images had an isotropic resampled resolution of 2x2x2 mm^3.

Voxel-wise main effect analysis was conducted using separate regressors for successful and unsuccessful trials and a vector with missed trials. In the Stop-Signal task we used separate regressors for Go and Stop trials together with seven regressors of no interest (six realignment parameters and a vector with missed trials) into a General Linear Model. For the Flanker task we used each condition (congruent and incongruent Go, NoGo) as separate regressors together with eight regressors of no interest (six realignment parameters, onsets of the feedback displays and a vector with missed trials) into a General Linear Model. To isolate the inhibition process, we calculated the contrast NoGo/Stop vs Go for both tasks using t-statistics. As supplementary analyses, we also report the results for the NoGo/Stop vs baseline (black fixation cross) contrast to be able to compare those with the

commonly used NoGo/Stop vs Go contrast, because the Go condition may include response control activity which could mask inhibitory activity (P. F. Liddle et al., 2001; Mostofsky and Simmonds, 2008; Simmonds et al., 2008). Results of these random-effects fMRI analyses are reported using $p < 0.0005$ uncorrected. As we were also interested in the common inhibition process across both tasks as well as in differences, we applied a conjunction analysis in addition to the between-task contrast using the inhibition contrasts of both tasks. We tested the contrasts of interest by a conjunction null hypothesis, a voxel-wise "logical AND" analysis (Nichols et al., 2005). Here we reported the results with $p < 0.005$ uncorrected.

Further, the contrast of interest was compared between the subgroups (fast: P300 < 300 ms and slow: P300 > 300 ms) activation clusters. To determine significant differences between the subgroups, we used second level t-statistics. The results reported correspond to a threshold of $p < 0.001$ uncorrected.

2.4 Results

2.4.1 Behavioral results

The accuracy in the Go condition was high in both tasks (Table 1). The lower accuracy in the Flanker task could be due to the additional incompatibility manipulation and the adaptive design of the task, enforcing speeded responses. The accuracies of the inhibition conditions

(NoGo and Stop) also differed between the tasks as expected. In the NoGo condition (Flanker) accuracy was 87.20% (±11.1%), whereas in the Stop condition (Stop) subjects had an accuracy of 50.08% (±3.6%) consistent with the adaptive tracking algorithm that elicits about 50% successful and 50% failed Stop trials in each subject. The mean reaction time of the correct Go condition was 401.14ms (±153.97ms) in the Stop-Signal task and 335.20ms (±15.57ms) in the Flanker task (see Table 1).

Regarding the group split in the Stop-Signal task, we found no significant differences between accuracy of the Go condition (slow, 97.45% (±1.57%); fast, 97.19% (±2.15%); t_{20} = -0.304; P= 0.764), accuracy of the Stop condition (slow, 49.83% (±4.99%); fast, 50.28% (±1.99%); t_{20} = 0.283; P= 0.780), mean reaction time of the Go correct condition (slow, 424.83ms (±217.21ms); fast, 388.29ms (±69.15ms); t_{20} = -0.552; P= 0.587), mean reaction time of the Stop incorrect condition (slow, 424.15ms (±219.31ms); fast, 381.97ms (±70.86ms); t_{20} = -0.631; P= 0.535) and mean stop-signal delay (slow, 251.37ms (±190.44ms); fast, 281.51ms (±97.50ms); t_{20} = 0.480; P= 0.637). Interestingly, the Stop-Signal reaction time (SSRT) showed a significant difference between the two groups (slow, 173.46ms (±49.35ms); fast, 106.78ms (±42.38ms); t_{20} = -3.411; P= 0.003). The SSRT was calculated by subtracting the average stop signal delay of successful inhibition from the average reaction time to Go signals (Williams et al., 1999). There was a significant correlation between the peak latency of the P300 and the

SSRT ($r = 0.49$; $P = 0.02$) (see Table 2; cf. Supplementary data Figure S4). The subscales inattention, hyperactivity and impulsivity of the Conners' Adults ADHD Rating Scale of the self- and observer report revealed no significant differences between the two subgroups.

Table 1: Descriptive statistics of behavioral variables

		Healthy subjects (n=15)		Statistics
Measure	Task	Mean	SD	df = 21
Accuracy Go [% correct]	Stop	97.30	1.87	t = 22.176
	Flanker	75.08	4.60	P < 0.001
Accuracy NoGo [% correct]	Stop	50.08	3.58	t = -15.017
	Flanker	87.20	11.05	P < 0.001
Mean Reaction time Go [ms]	Stop	404.90	151.89	t = 2.202
	Flanker	335.20	15.57	P = 0.39

Table 2: Statistical performance measures of the two subgroups

				Statistics
Measure	Condition	Mean	SD	t-Values (df = 20)
Accuracy Go [% correct]	slow group	97.45	1.57	*t = -0.304*
	fast group	97.19	2.15	*P = 0.764*
Accuracy Stop [% correct]	slow group	49.83	4.99	*t = 0.283*
	fast group	50.28	1.99	*P = 0.780*
Mean reaction time Go [ms]	slow group	424.83	217.21	*t = -0.552*
	fast group	388.29	69.15	*P = 0.578*
Mean reaction time Stop unsuccessful [ms]	slow group	424.15	219.31	*t = -0.631*

	fast group	381.97	70.86	*P = 0.535*
Mean Stop-Signal delay [ms]	slow group	251.37	190.44	*t = 0.480*
	fast group	281.51	97.50	*P = 0.637*
Stop-Signal reaction time (SSRT) [ms]	slow group	173.46	49.35	***t = -3.411***
	fast group	106.78	42.38	***P = 0.003***

Note: slow group: P300 > 300ms; fast group: P300 < 300ms

2.4.2 ERP results

2.4.2.1 Stop-Signal Task

In the Stop-Signal task, mean P300 amplitude (200-600 ms) of the Stop condition revealed a pronounced centro-parietal positivity (Figure 2 A) that extended to the Cz electrode ($t(21) = 11.24$, $p < 0.001$). The latency of the P300 peak was detected after 376ms with corresponding mean peak amplitude 6.80 µV. Based on the individual P300 peak latencies we split up the subjects into two subgroups: a fast group with a P300-peak < 300ms and a slow group with a P300-peak > 300ms. The mean P300 peak latency of the fast group was 279 ms at Cz ($t(11) = 7.37$, $p < 0.001$) with a mean peak amplitude of 6.93 µV. The slow group showed a mean peak latency of the P300 at Cz ($t(9) = 8.75$, $p < 0.001$) after 493 ms with a mean peak amplitude of 6.64 µV. The two subgroups revealed a significant difference of their latency (by definition, $t(20) = -6.57$, $p < 0.001$), but no difference between the P300 amplitude at their respective peak ($t(20) = 0.236$, $p = 0.816$). The Go condition showed no significant differences of latency and amplitude between the two subgroups (see Figure 3 A/B).

2.4.2.2 NoGo-Flanker Task

The mean amplitude of the NoGo P300 (200-600 ms) revealed a pronounced centro-parietal positivity (Figure 2 B) extends to Cz ($t(21) =$

10.05, $p < 0.001$). The mean P300 peak latency was detected after 413 ms with corresponding mean peak amplitude of 6.77 μV. When comparing the results of the fast and the slow Stop task P300 subgroups, the mean Flanker task NoGo P300 amplitude (($t(20) = -0.397$, $p = 0.695$) as well as the latency ($t(20) = 0.443$, $p = 0.663$) did not differ significantly (see Figure 3 C).

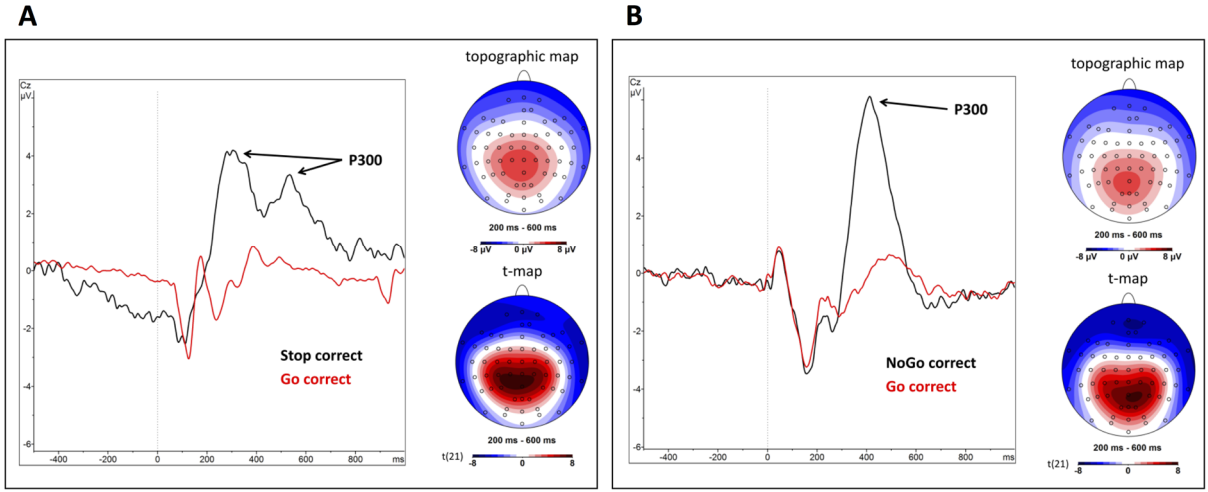


Figure 2: A: Stop-Signal task: Grand average ERP of Stop condition (black line) at electrode Cz and corresponding topographical map and t-map (200-600ms). The grand average of the Go condition is represented by the red line. B: Flanker task: Grand average ERP of NoGo condition (black line) at electrode Cz and corresponding topographical map and t-map (200-600ms). The grand average of the Go condition is represented by the red line. Topographical t-maps of the NoGo/Stop vs Go condition of both tasks are illustrated in supplementary Figure S6.

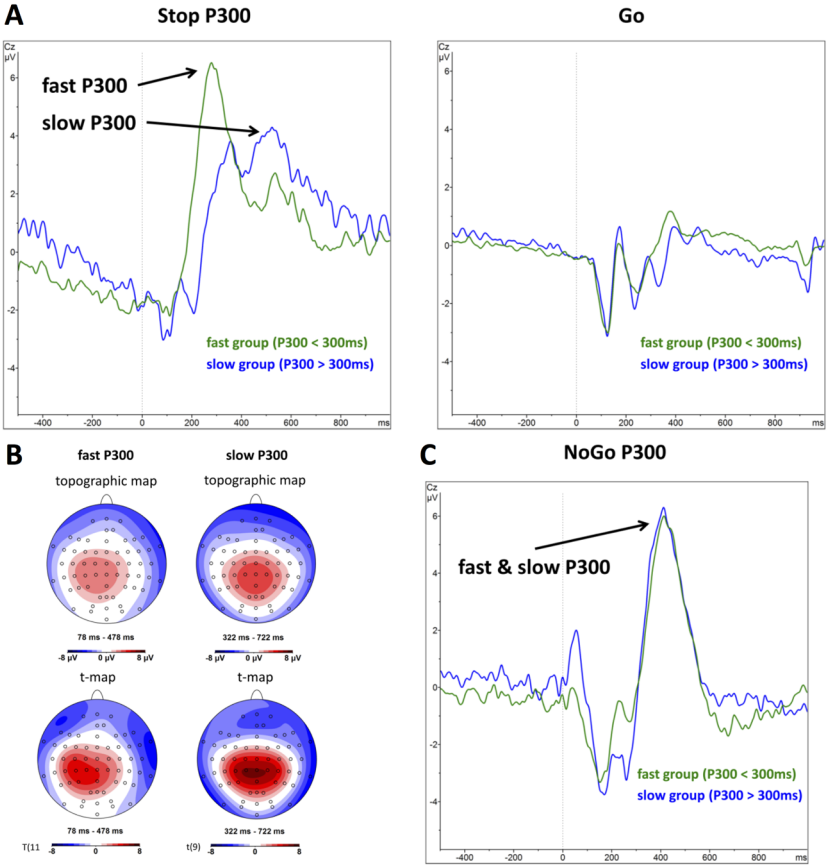


Figure 3: Results of the subgroup split. A: Stop-Signal task: Grand average ERP of Stop and Go condition at electrode Cz for the slow group (blue: P300 > 300ms) and the fast group (green: P300 < 300ms). B: Corresponding topographical maps and t-maps (Stop vs zero). C: Flanker task: Grand average ERP of NoGo and Go condition at electrode Cz for the slow group (blue: P300 > 300ms) and the fast group (green: P300 < 300ms).

2.4.3 fMRI results

2.4.3.1 Main effects

The Stop-Signal task revealed activation of the inhibition condition (Stop correct vs. Go correct) within inhibitory regions in both hemispheres in bilateral IFG, insula, pre-SMA/ACC/superior frontal gyrus, middle and superior temporal gyri. Additional activated regions resulted in the left fusiform gyrus, left middle occipital gyrus, left supramarginal gyrus and the right precuneus (see Figure 4 A; Table 3).

In the Flanker task, our main effect analysis of inhibition (NoGo correct vs. Go correct) showed activations in the left and right IFG, the bilateral superior frontal gyrus and the left middle frontal gyrus / pre-supplementary motor area. Further activations were found in the left supramarginal gyrus as well as in the left and right inferior parietal lobule (IPL) (see Figure 4 B; Table 3). Differences in activation for the main contrast NoGo/Stop vs Go between the Flanker and the Stop tasks are illustrated in supplementary Figure S1.

The supplementary results for the NoGo/Stop vs baseline (black fixation cross) contrast largely agreed with the commonly used NoGo/Stop vs Go contrast (cf. Supplementary data Figure S2). Activations in the pre-SMA also appeared when inhibition in the Flanker task was contrasted to baseline, but remained less prominent than for the Stop task.

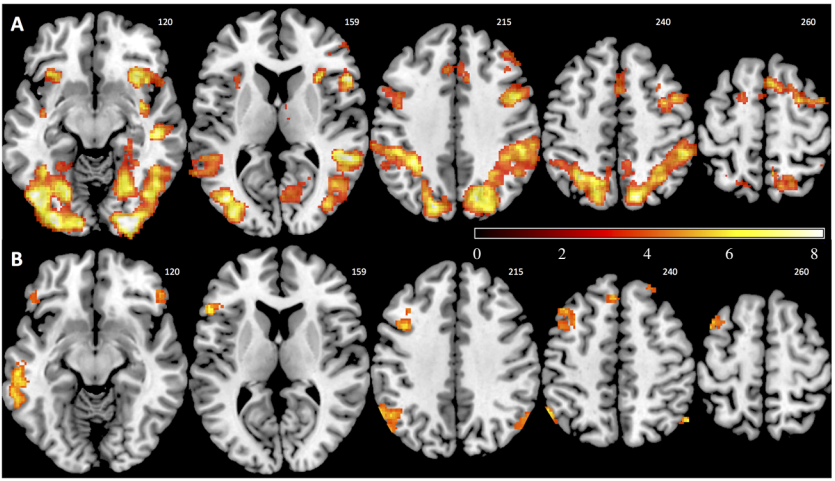


Figure 4: Main fMRI results of response inhibition: **A:** Stop-Signal task: Activation map of the successful Stop condition (Stop vs Go contrast). **B:** Flanker task: Activation map of the successful NoGo condition (NoGo vs Go contrast). Results are reported using $p<0.0005$ uncorrected. Color bar indicates t-values.

2.4.3.2 Common results across task

Conjunction analysis between the inhibition conditions of the Flanker and Stop-Signal tasks showed common bilateral clusters in the IFG, the inferior temporal gyrus, the middle temporal gyrus and the supramarginal gyrus. Additional common task activations were found in the right IPL and the right DLPFC (see Figure 5, Table 3). We also analyzed the conjunction results for the contrast NoGo/Stop vs baseline (cf. Supplementary data Figure S3 and Table S1).

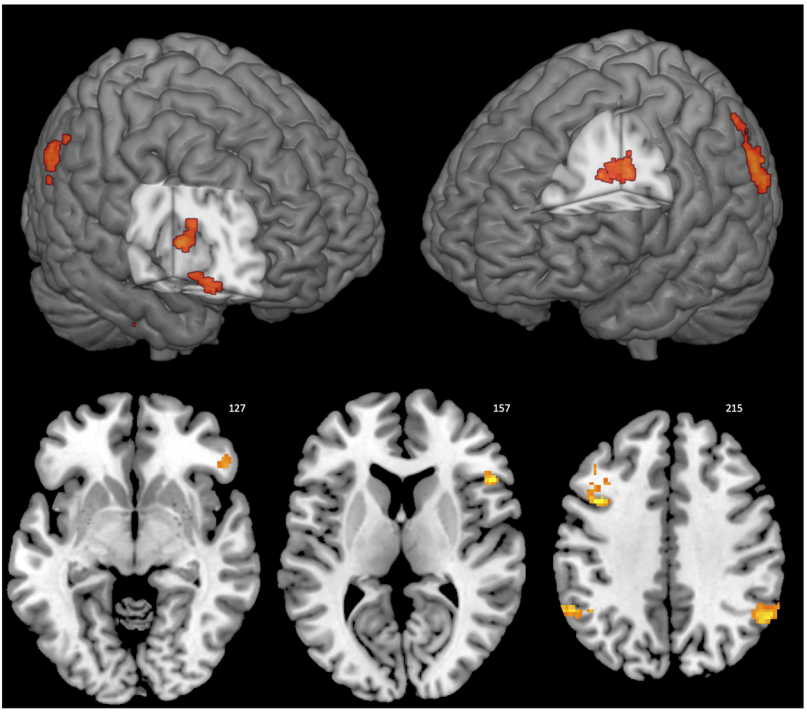


Figure 5: Results of the conjunction analysis of the inhibition condition of both tasks. Data of the NoGo (Flanker) and Stop (Stop-Signal) contrast were used. Results are reported using p<0.005 uncorrected. Color bar indicates t-values.

2.4.3.3 Subgroup results

Our group split according to Stop P300 latency did not indicate any significant subgroup differences in the Flanker task. For the Stop task significant activation differences were found only in the fast vs slow responders comparison, with specific differences between subgroups in

the frontal lobe. The fast group in comparison to the slow group showed activations in the dorsal and ventral ACC, left IFG and the right hippocampus (see Figure 6; Table 3; for the overlay of both sub-groups see Supplementary data Figure S5).

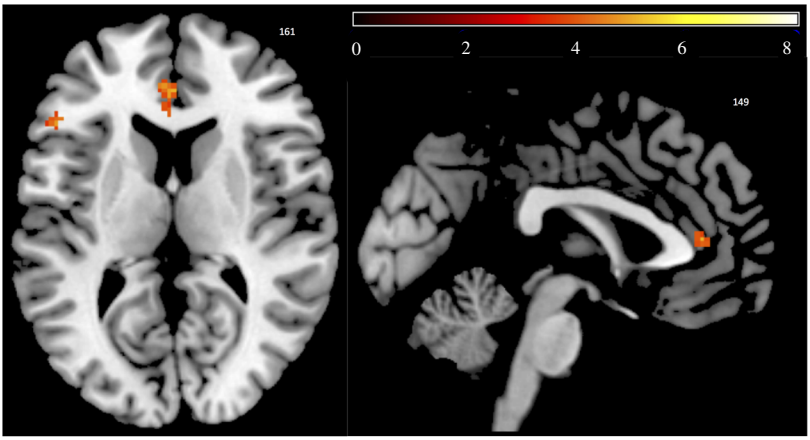


Figure 6: Results of the fMRI group split. Stop-Signal task: Stop conditions (Stop vs Go contrast) are shown for the group contrast fast group (P300 < 300ms) vs slow group (P300 > 300ms). Results are reported at p<0.0005 uncorrected.

Table 3: fMRI peak activations for the inhibition contrast

					MNI coordinates				
Task	Contrast	Region	Hemisphere	Cluster size (voxels)	x	y	z	t score	z score
Flanker	NoGo vs. Go	Inferior Frontal Gyrus	Left	81	-54	24	10	6.57	4.84
		Inferior Frontal Gyrus	Right	98	52	-4	-36	6.56	4.83
		Middle Temporal Gyrus	Left	554	-62	-42	-8	6.46	4.79
		Supramarginal Gyrus	Left	750	-48	-56	32	6.28	4.71

		Inferior Lobule	Parietal	Left		-52	-58	40	5.93	4.53
		Inferior Lobule	Parietal	Right	230	54	-64	40	5.00	4.04
		Inferior Gyrus	Frontal	Right	61	50	36	-12	5.99	4.57
		Middle Gyrus / pre-SMA	Frontal	Left	378	-38	10	36	5.78	4.46
		Superior Gyrus	Frontal	Bilateral	38	-2	32	52	5.68	4.41
		Nodule		Left	32	-6	-46	-36	5.17	4.14
		Inferior Gyrus	Frontal	Left	44	-46	32	-12	4.69	3.86
Stop	Stop vs.	Fusiform Gyrus		Left	4827	-42	-54	-16	11.3	6.45

Go							7	
	Middle Occipital Gyrus	Left		-50	-74	0	10.48	6.22
	Middle Occipital Gyrus	Left		-42	-68	-6	9.11	5.80
	Precuneus	Right	7021	24	-92	-8	11.06	6.37
	Middle Temporal Gyrus	Right		46	-68	4	10.35	6.18
	Superior Temporal Gyrus	Right		54	-42	8	9.39	5.89
	Inferior Frontal Gyrus / Insula	Right	1665	36	24	-2	10.83	6.31
	Inferior Frontal	Left	461	-36	22	4	10.0	6.09

	Gyrus / Insula						2	
	Inferior Frontal Gyrus	Left		-30	18	-14	7.60	5.27
	Insula	Right	51	36	-4	-12	8.04	5.43
	Middle Frontal Gyrus	Right	550	40	36	18	7.70	5.31
	Superior Frontal Gyrus	Right		30	52	20	5.84	4.49
	Middle Temporal Gyrus	Left	269	-54	-54	2	7.55	5.25
	Superior Temporal Gyrus	Left		-56	-42	12	6.25	4.69
	Superior Temporal Gyrus	Right	42	52	12	-18	6.65	4.87
	Cingulate Gyrus /	Bilateral	265	4	22	44	6.50	4.80

		pre-SMA							
		Precuneus	Right	55	6	-48	54	6.09	4.61
		Superior Frontal Gyrus/ pre-SMA	Right	57	6	14	60	6.08	4.61
		Medial Frontal Gyrus / pre-SMA	Right		14	8	56	5.25	4.18
		Precentral Gyrus	Left	110	-46	-2	40	5.44	4.28
		Inferior Frontal Gyrus	Left		-50	10	16	5.39	4.26
		Lingual Gyrus	Bilateral	58	0	-80	-2	6.04	4.59
		Supramarginal Gyrus	Left	92	-56	-46	32	5.07	4.08
Conjunc-tion	NoGo/Stop vs. Go	Inferior Temporal Gyrus	Right	62	48	-4	-36	4.36	3.95

	Middle Temporal Gyrus	Right		44	4	-38	4.14	3.78
	Supramarginal Gyrus	Left	246	-64	-56	24	3.87	3.57
	Inferior Frontal Gyrus	Left	91	-42	10	38	3.89	3.59
	Middle Frontal Gyrus	Left		-36	22	36	3.66	3.40
	Inferior Parietal Lobule	Right	225	54	-56	40	3.76	3.48
	Supramarginal Gyrus	Right		48	-46	34	3.70	3.43
	Inferior Frontal Gyrus	Right	41	50	22	8	3.71	3.45
	Nodule	Bilateral	79	-4	-46	-38	3.55	3.31

		Inferior Frontal Gyrus	Right	38	46	38	-12	3.21	3.03
Stop	Stop vs. Go fast vs. slow	Hippocampus	Right	30	30	-26	-10	5.93	4.45
		Inferior Frontal Gyrus	Left	32	-48	28	8	5.65	4.32
		Anterior cingulate cortex	Left	59	-12	46	4	4.36	3.61

Note: Results are reported using $p<0.0005$ uncorrected; $k>30$ for Flanker (NoGo vs. Go) and Stop (Stop vs. Go), $p<0.005$ uncorrected; $k>30$ for the conjunction results and $p<0.0005$ uncorrected; $k>30$ for the Stop subgroups (Stop vs Go, fast vs slow).

2.5 Discussion

Here, we used simultaneous EEG-fMRI recordings to disentangle temporal and spatial aspects of response inhibition in two tasks. Our results identified a common inhibition network across tasks and clarify the temporal aspects of response inhibition. We showed that the right and left IFG as well as the left DLPFC play an important role in the frontal network of response inhibition. Interestingly, the temporal resolution of the EEG enabled us to define subgroups that are correlated with the SSRT and differed in frontal lobe activation upon inhibition trials. Moreover, we were able to show that ERP latency differences of the Stop P300 across subgroups of individuals correspond to different fMRI activations in the anterior cingulate cortex and the left IFG.

In line with previous findings our whole brain fMRI results of both tasks showed activation of the response inhibition condition in frontal regions such as right and left IFG, superior and middle frontal gyrus, the left and right insula and the pre-SMA/ACC (Swick et al., 2011). The Flanker task showed no significant activations in the insula and a smaller cluster in the pre-SMA than the Stop task. As the task designs differ in temporal and visual aspects of stimulus presentation, different stimulus detection and interpretation processes are required that are quite difficult to disentangle (Criaud and Boulinguez, 2013). It has been suggested that the variety of activated regions in the frontal cortex during response inhibition may be explained by differences in task design (Mostofsky and Simmonds, 2008). The Stop task with its track-

ing design seems to have a higher load on response inhibition, while the Flanker task has a higher load on the response selection. To withhold an already triggered and possibly initiated response selection of the Go stimulus in the Stop task seems to be more difficult than the response selection in the Flanker task and results in a higher load on response inhibition. These differences of difficulty and load may explain the stronger pre-SMA activation in the Stop task which was retained in the supplementary inhibition-baseline contrast also yielding some pre-SMA activation in the NoGo-Flanker task as expected (P. F. Liddle et al., 2001; Mostofsky and Simmonds, 2008; Simmonds et al., 2008). These findings further support an interpretation in terms of increased inhibitory load in the Stop-Signal task. Furthermore, the differences in stimulus order and size may also account for the altered activation in the visual cortex and in temporal and parietal regions although the inhibition contrast controls for basic sensory effects (cf. Supplementary data Figure S1). The task specific insular activation could indicate the maintenance of task rules and readiness (Swick et al., 2011) and depend on a combination of intentional and response control demands (Dodds et al., 2010). Both tasks involve the go and the inhibition sub-tasks but differences in relative importance could result in specific activation patterns (Baria et al., 2013).

The conjunction analysis showed that especially right IFG and the left middle frontal gyrus / DLPFC belong to a common response inhibition network across tasks. Additional activation clusters in the inferior /

middle temporal gyrus and the supramarginal gyrus seem to be part of a common attention and task-maintenance network (Chambers et al., 2009). There were no significant overlapping clusters in the pre-SMA in the conjunction analysis of the Stop and the Go/NoGo paradigm. These results of the conjunction analysis thus contrasts somewhat with the suggestion that the pre-SMA is an essential region for inhibition in several response inhibition tasks (Swick et al., 2011), especially because both tasks showed activation that extends to the pre-SMA. It is feasible that the two tasks activated slightly different subregions of the pre-SMA due to the different weighting of specific aspects of processing and/ or different functions involved: In the Stop trials e.g. the inhibition of a previously selected and initiated response has to be inhibited while this is not the case for the Nogo-Flanker condition where a specific response is primed by the flankers and the more frequent occurrence of Go trials but still is not initiated. Still, our results confirm that the right IFG is commonly used to initiate response inhibition. Further regions in the insula and pre-SMA are part of the frontal inhibition network, but their integration in the inhibition process seems to be task dependent (Mostofsky et al., 2003).

The fact that the pre-SMA is not uniquely required for inhibition across tasks is supported by our study design that the same subjects performed both tasks within 20 minutes. Even though also this design cannot fully exclude differences in fatigue or motivational states of the subjects between the tasks, most variability should have been minimized, and the typical ERP and fMRI differences between the two

tasks argue against confounding effects of the fixed order. Hence, we propose a model in which the pre-SMA together with the IFG is required for response inhibition, but its contribution is task dependent. Especially the Flanker task and its Go/NoGo paradigm may evoke a stronger response selection than the Stop-Signal task that could result in different pre-SMA activations (Simmonds et al., 2008). Moreover, we showed that even the subjects' task performance could affect the spatial activation of the pre-SMA. This evidence will be discussed next.

The ERPs of both tasks revealed the expected positive P300 enhancement during the inhibition condition at central electrodes (Bokura et al., 2001; Bruin et al., 2001; Falkenstein et al., 1999; Pfefferbaum et al., 1985). However, in both tasks the distribution of the P300 was posterior to the electrode Cz (but still anterior to the Go P300). The P300 of the Stop task showed two distinct peaks. Based on this temporal variation, we investigated the individual peak latency of the P300. This analysis characterized two subgroups with a difference in the latency (slow: 493 ms; fast: 279 ms) of the centrally positive P300 peak. The same group split resulted in no differences of the NoGo P300 latency (or amplitude) in the Flanker task. Smith and colleagues (Smith et al., 2006) already showed that the NoGo P300 effect was larger in fast responders than in slow responders. Interestingly, the task performance data of the Stop task showed significant differences only for the SSRT between the subgroups, while accuracy, reaction times

and mean stop-signal delays did not differ. These behavioral performance results suggest that the P300 peak differences are selectively based on the efficiency of response inhibition. The significant positive correlation between the P300 latency and the SSRT confirms the relations to neural mechanisms of response inhibition (Wessel and Aron, 2015). The fact that the subgroups are only differentiated by the SSRT (and not by other aspects of performance such as Go accuracy or reaction time) may partly reflect the adaptive design of the Stop task, but could also indicate that these subgroups rely on different strategies (Leotti and Wager, 2010). Hence, these individual strategies lead to different neural processes that are not discoverable by less specific measures of task performance. The finding of subgroups of individuals with different temporal neural processes is a novel approach and should be taken into account while studying individual differences of brain mechanisms.

The evidence for individual variability of neuronal patterns reflecting specific inhibitory aspects of task performance is in line with Wessel and Aron (Wessel and Aron, 2015). Similarly, we focused on the high temporal resolution of the ERP to cluster subgroups of different Stop P300 peak latencies. However, we used a novel reverse approach starting with neurophysiological subtyping to characterize individual differences. It is difficult to say whether these differences are based on different task strategies or other aspects of normal individual variability of the inhibition process. However, the high temporal resolution of the EEG gave us an additional perspective on individual differences of

neuronal mechanisms.

A core advantage of our study is the combined recording of EEG and fMRI to localize individual differences in neurophysiological timing of response inhibition and its underlying prefrontal activation clusters. Similar to the P300 latency differences, the subgroup split in the fMRI data revealed different activation clusters in the prefrontal cortex.

Of particular interest are effects in regions surrounding the pre-SMA as its role in inhibition seems to be time-specific (Verbruggen and Logan, 2008b). Subjects who had a P300 peak before 300 ms showed an activation cluster in the ventral and dorsal anterior cingulate cortex and the left IFG compared to subjects with a P300 peak after 300 ms (fast vs slow responders). We did not find any significant activation cluster vice versa (slow vs fast responders). We already discussed the function of brain regions surrounding the pre-SMA and its task-specific activations. Here, we showed that the ACC and the left IFG represent inter-individual differences of task performance. Hence, the activation in the ACC appears to be driven by several sources and a combination of attention, working memory or response selection processes (Criaud and Boulinguez, 2013; Simmonds et al., 2007) which vary across task-specificity, task strategy or subject variability. These findings and the novel approach of subgroup classification are important in interpretation of group differences since there are several studies that showed differences in inhibition in neurological and psychiatric diseases (Chambers et al., 2009) such as attention deficit hyperactivity disorder

(ADHD) (Aron et al., 2003; Rubia et al., 2001; 1999; van Rooij et al., 2015). Especially group classification in heterogeneous disorders such as ADHD (Nigg et al., n.d.; Sonuga-Barke, 2002) may benefit from these results to detect interindividual activation differences. Moreover, these frontal regions are part of the default mode network or the cognitive control network (Zhang and Raichle, 2010) that play a central role in several psychiatric diseases (Fox, 2010). We recommend a careful interpretation of group differences in response inhibition tasks considering that task design and subject variability of task performance have considerable effects.

2.6 Conclusion

In conclusion, our simultaneous EEG-fMRI approach revealed common activations related to inhibition in the two most often used response inhibition tasks. We showed that the right IFG seems to play a major role in inhibition across both tasks. Moreover, the temporal resolution of the EEG provided further insights into the neural correlates of task specific interindividual variability of inhibitory timing. We were able to show that ERP latency differences of the Stop P300 across subgroups of individuals correspond to different fMRI activations in the anterior cingulate cortex and the left IFG. These findings are based on EEG informed fMRI and could be useful for interpreting (sub)group differences in the timing of response inhibition. Future studies should consider whether such variability in neurophysiological timing of inhi-

bition is associated with frontal activation and underlies inhibitory deficits in clinical groups, and how such variability can account for interindividual differences in psychiatric diseases with strong heterogeneity such as ADHD.

2.7 Supplementary Material

S1: Task differences of inhibition contrast

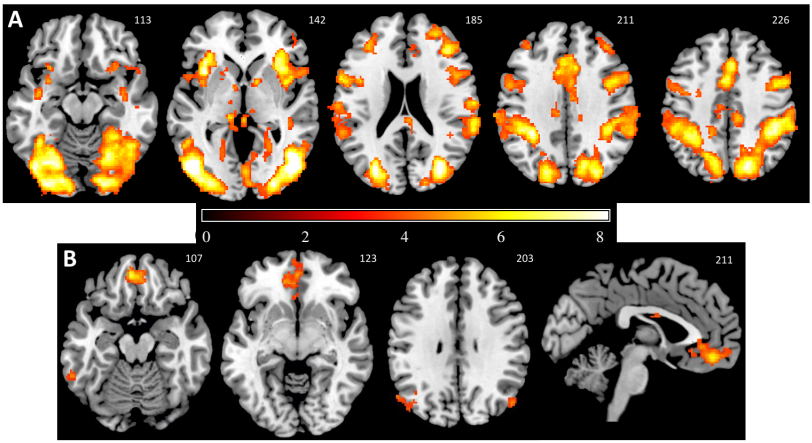


Figure S1: Task differences of the inhibition contrast: **A:** Stop-Signal task vs Flanker task activation map. **B:** Flanker task vs Stop-Signal task activation map. Results are thresholded using $p<0.0005$ uncorrected. Color bar indicates t-values.

S2: Inhibition contrast NoGo/Stop vs Baseline

An important issue in response inhibition is the choice of the inhibition contrast. Most fMRI studies selected the contrast NoGo/Stop vs. Go which is useful to subtract visual activation and other task-related cognitive processes used similarly for Go an NoGo trials. However, others have suggested that the pre-SMA plays important but different roles in Go and NoGo trials. During Go trials the pre-SMA might be related to response selection processes while during NoGo trials the same area has been implicated with inhibition of response selection (Mostofsky

and Simmonds, 2008; Simmonds et al., 2008) with the same neurons participating in inhibition and response selection (Isoda and Hikosaka, 2007). Thereby, an area jointly active during Go and inhibition trials, though important for inhibitory processes may not show up in the NoGo/Stop vs Go contrast. In the supplementary figures S2 and S3 we thus show additionally the activation clusters of the contrasts Stop vs baseline for the Stop-Signal task (Figure S2A), NoGo vs baseline for the Flanker task (Figure S2B) and also the conjunction analysis for both tasks using the contrast NoGo/Stop vs baseline (Figure S3).

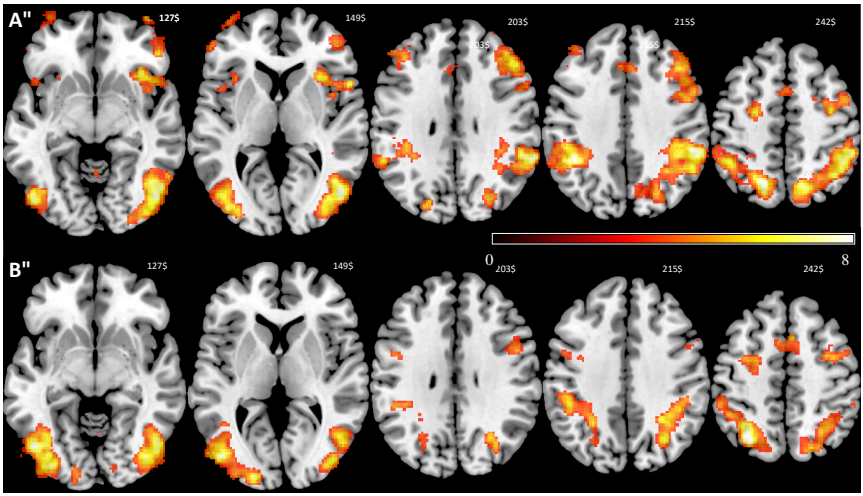


Figure S2: fMRI results of response inhibition contrast Stop/NoGo correct vs baseline **A:** Stop-Signal task: Activation map of the successful Stop condition (Stop vs baseline). **B:** Flanker task: Activation map of the successful NoGo condition (NoGo vs baseline). Results are thresholded using $p<0.0005$ uncorrected. Color bar indicates t-values.

S3: Conjunction analysis NoGo/Stop vs Baseline

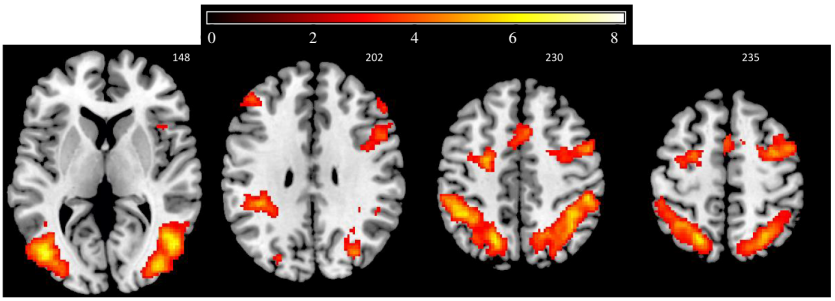


Figure S3: Results of the conjunction analysis of the inhibition contrast NoGo/Stop vs baseline of both tasks. Data of the NoGo (Flanker) and Stop (Stop-Signal) contrast were used. Results are thresholded using $p<0.005$ uncorrected. Color bar indicates t-values.

Table S1: fMRI peak activations of the conjunction analysis

					MNI coordinates				
Task	Contrast	Region	Hemisphere	Cluster size (voxels)	x	y	z	t score	z score
Conjunction	NoGo/Stop vs. Baseline	Inferior Temporal Gyrus	Right	8548	48	-72	-4	7.06	5.74
		Middle Temporal Gyrus	Right		48	-55	2	7.03	5.72

		Middle Occipital Gyrus	Left		-45	-72	2	7.02	5.72
		Precuneus	Left	2642	-18	-66	50	6.44	5.37
		Inferior Parietal Lobule	Left		-44	-38	35	5.05	5.13
		Inferior Parietal Lobule	Right	2744	48	-36	46	6.31	5.29
		Middle Frontal Gyrus	Left	601	-24	-6	48	5.25	4.60
		Middle Frontal Gy-	Right	1261	32	0	52	5.25	4.60

		rus							
		Medial Frontal Gy-rus	Bilateral	396	2	10	52	4.51	4.07

Note: Results are thresholded using $p<0.005$ uncorrected; $k>30$.

S4: Correlation of the SSRT and the NoGo P300 peak latency

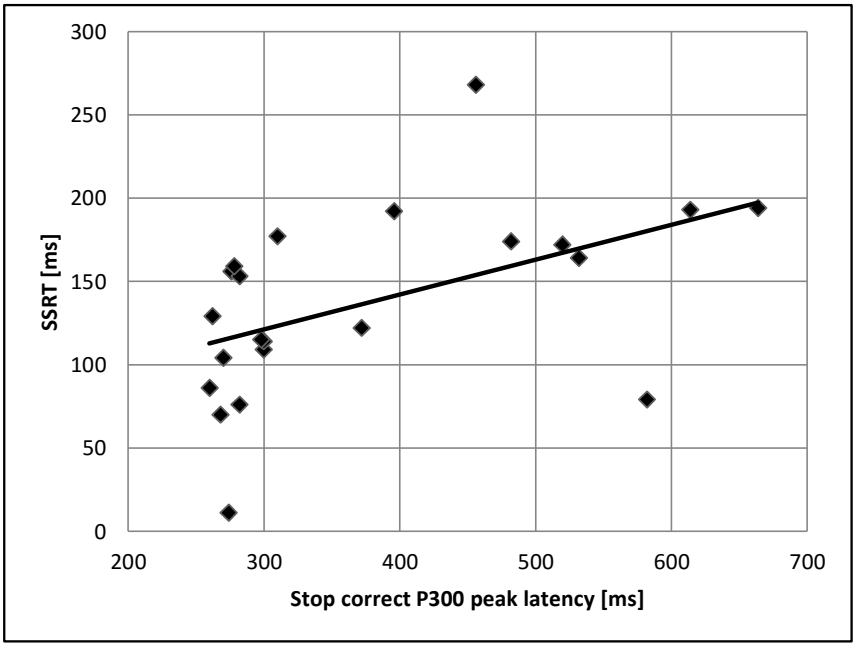


Figure S4: Correlation between the SSRT and the Stop correct P300 peak latency. Pearson- Correlation 0.49, p = 0.02.

S5: Overlap of activation of fast and slow P300 subgroups of the Stop task

Our group split according to Stop P300 latency did not indicate any significant subgroup activation differences in the two-sample t-test for the Flanker task but yielded several regions with enhanced activation in the slow P300 group (cf. Figure 6, main text). For a better illustration of subgroup differences in the Stop tasks, an overlay image is

given below showing the differences between these two groups within the frontal lobe. The fast group showed activations in the lower part of the bilateral anterior cingulate, the bilateral cingulate and medial frontal gyrus as well as in the right superior frontal gyrus / pre-SMA. In contrast the slow group just showed an activation cluster in the upper part of the bilateral cingulate gyrus / pre-SMA.

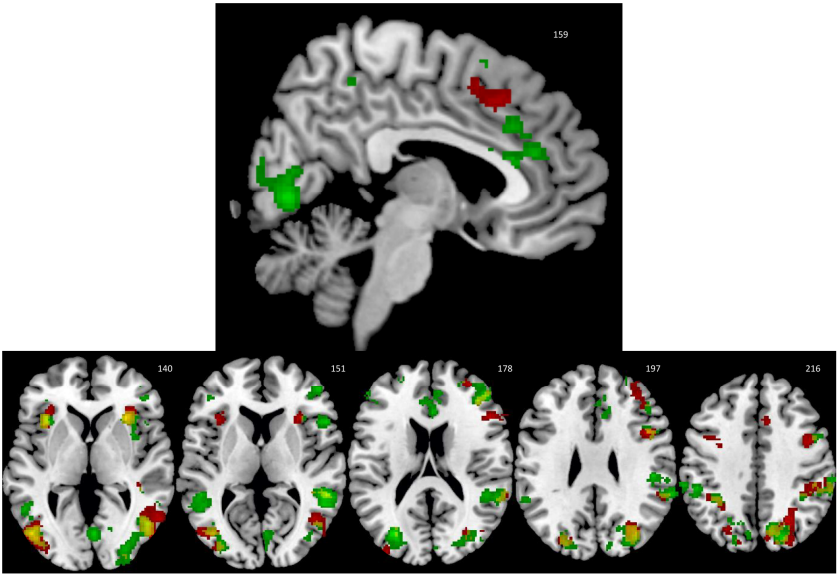


Figure S5: Results of the fMRI group split. Stop-Signal task: Stop conditions (Stop vs Go contrast) are shown for the slow group (red: P300 > 300ms) and the fast group (green: P300 < 300ms). Yellow color indicates overlap of the two groups. Results of the contrasts are illustrated using a $p<0.0005$ uncorrected.

S6: Topographical t-maps of NoGo/Stop vs Go conditions

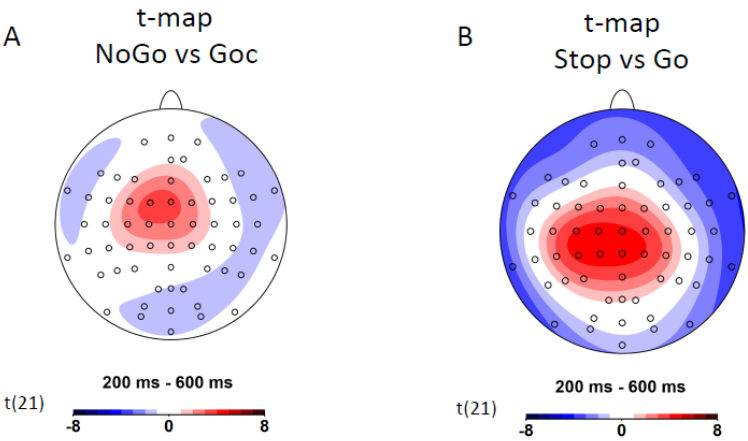


Figure S6: Topographical t-maps (200-600ms) of Flanker task (A) and Stop-Signal task (B).

Acknowledgment

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Conflict of interest

The other authors declare no potential conflicts of interest.

3 Study B

State-dependent functional connectivity alterations in children with ADHD

Anthony Schläpfer[1,2], Thomas Koenig[3], Daniel Brandeis[1,2,4,5,*]

[1] Department of Child and Adolescent Psychiatry and Psychotherapy, Psychiatric Hospital, University of Zürich

[2] Neuroscience Center Zurich, University of Zurich and ETH Zurich, Zürich, Switzerland

[3] Translational Research Center, University Hospital of Psychiatry and Psychotherapy, University Bern Psychiatric Services (UPS) Bern, Switzerland

[4] Zurich Center for Integrative Human Physiology (ZIHP), University of Zurich, Zürich, Switzerland

[5] Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim/Heidelberg University, 68159 Mannheim, Germany

3.1 Abstract

Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent developmental disorders. Recent models have shifted the focus from regional brain abnormalities to dysfunction in network organization. It has been suggested that interaction between the default mode network (DMN) and the task-positive network is altered in children with ADHD. The deactivation or suppression of the DMN with task performance was reported to be reduced in ADHD. However, little work has compared the DMN activity across different cognitive states (resting vs task state) in children with ADHD. Here, we investigated the functional network connectivity (FNC) during resting state and an inhibition task between children with ADHD and a healthy control group. We focused on the FNC between subcomponents of the DMN and brain regions, which are involved in the executive process of inhibition (cognitive control network (CCN), somatomotor network (SMN)). In the resting state the FNC showed significant group differences between anterior and posterior parts of the DMN and regions related to the SMN. In the task state only the FNC between the posterior part of the DMN and the CCN differed significantly in children with ADHD and the control group. Both states contained FNC pairs with lower as well as higher anti-correlation in children with ADHD. This could be explained by the parcellation of the DMN and emphasize the importance of considering subcomponents in functional networks.

Furthermore, the clinical ADHD scores correlated with the FNC, reflecting severity-related attenuation of the anti-correlation in children with ADHD. Even though the reduced DMN attenuation and some other ADHD-related deviations held across states, other results illustrate that most deviations in subcomponents of the networks and their FNC are state-dependent. This study highlights the importance of considering functional connectivity and functional networks subcomponents across different cognitive states in psychiatric disorders.

3.2 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder (Castellanos et al., 2002; Fair et al., 2010; Matthews et al., 2014), which has long been thought to reflect dysfunctions in specific regions that subserve cognitive, motor and attentional functions (Bush, 2009). To date, much of our understanding of brain functions in ADHD rests on regional task-specific alterations. Recent models have shifted the focus from regional brain abnormalities to dysfunction in network organization, considering also resting states. Posner and colleagues (Posner et al., 2014) showed evidence that even at rest functional connectivity of children with ADHD deviates in both executive attention and emotional regulation circuits while emphasizing the importance to explore multiple neural networks. Especially the study of the pathophysiology of neuropsychiatric diseases such as ADHD in-

creasingly focuses on the interaction of several brain regions to look at neural networks (Castellanos and Proal, 2012; Fair et al., 2010; Konrad et al., 2006; Posner et al., 2014). It is suggested that such neural connectivity deficits might contribute directly to inattention, impulsivity and other ADHD symptoms (Liston et al., 2011). Most of these studies used resting state data to compare such functional network organizations.

So far, several networks with atypical functional network connectivity (FNC) have been found. The most prominent network and its association with ADHD is the default mode network (DMN) (Castellanos et al., 2008; Fair et al., 2010; Sun et al., 2012; Uddin et al., 2008). The DMN, initially reported by Raichle and colleagues (Raichle et al., 2001) extends along the anterior-posterior and inferior-superior axes (Buckner et al., 2008; Harrison et al., 2008) and includes the precuneus, the posterior cingulate cortex (PCC), the medial prefrontal cortex (MPFC) and the lateral, medial and inferior parietal cortex. It shows higher activity in absence of a task and it becomes deactivated during a cognitive state with a goal-directed task (Buckner et al., 2008; Raichle and Snyder, 2007). The DMN activity is attenuated but not absent during the transition from rest to a task state (Eichele et al., 2008; Greicius and Menon, 2004). The transition from rest to a task state and its deactivation or suppression of the DMN is associated with momentary lapses in attention and less accurate performance in an attentional control task (Weissman et al., 2006). These findings suggest that a defec-

tive transition of the DMN during rest and task state lead to failures in attentional demands (Posner et al., 2014). Misconfigurations of the DMN during the transition of different states may interfere with task-relevant attentional networks that would be mirrored on the behavioral level by performance deficits such as increase of reaction times and frequency of errors (Konrad et al., 2006) often seen in patients with ADHD. The group of Fair (Fair et al., 2010; 2008) also investigated the developmental aspects of connections within the DMN and showed that subjects with ADHD show weaker correlations in connections, which tend to increase with development and vice versa. Consequently it has been suggested that ADHD could be considered a DMN disorder (Sonuga-Barke and Castellanos, 2007b), although dysfunction of the DMN has also been reported in several other mental disorders such as dementia, schizophrenia, depression, anxiety, epilepsy and autism (Broyd et al., 2009).

The DMN is typically anti-correlated with the cognitive control network (CCN) also termed task positive network, which encompasses the dorsal anterior cingulate cortex or supplementary motor are (SMA), dorsolateral prefrontal cortex (DLPFC), inferior frontal junction, anterior insular cortex and posterior parietal cortex and is involved in executive cognitive processes such as working memory and inhibitory control (Cole and Schneider, 2007). The CCN shows more activation during tasks, and its regions appear to be associated with increased

alertness, response preparation or selective attention (Fox et al., 2005; Sonuga-Barke and Castellanos, 2007b). Anterior regions of the CCN which have a critical role in attention, executive processing, response selection, error detection or response inhibition have been suggested to influence behavioral inhibition in children with ADHD (Bush, 2009).

The DMN and CCN show anti-correlated behavior in many different rest and task states (Fox et al., 2005; Grady et al., 2010; Raichle et al., 2001). Castellanos and colleagues (Castellanos et al., 2008) observed this anti-correlation at rest between central regions of the DMN (precuneus, PCC) and regions of the CCN such as the dorsal anterior cingulate cortex (dACC), the right inferior frontal gyrus (rIFG) and the right medial frontal gyrus in both adults with ADHD and healthy control participants. However, the extent of the anti-correlation between the DMN and CCN was weaker in the adult ADHD group. Especially the long-range connections between the dACC and the precuneus/PCC, two important hubs of the brain, were affected. These results may be interpreted as a modulation error of the DMN that interferes with normal functioning of the CCN during a cognitive state as the DMN "staying" in its resting state may result in attentional lapses (Weissman et al., 2006). Analogous findings were reported in four additional studies: The first study found a decreased negative functional correlation (anti-correlation) during resting state in adolescents with ADHD compared to a healthy control group between the dACC and the DMN (dorsomedial prefrontal cortex, PCC). The authors suggested that this

decreased anti-correlation may be an abnormal balance between attentional control and internal thought (Sun et al., 2012). A second study focused on the correlation of the dACC and the PCC. Here, a machine-learning algorithm to classify adults with ADHD indeed indicated a significantly abnormal pattern of this correlation in the ADHD group. Moreover, the correlation of the dACC and the PCC was more similar to the patterns of younger controls (Sato et al., 2012). This findings suggests a possible maturational delay of the dACC-PCC connectivity in ADHD (Posner et al., 2014). A third study showed that at rest the DMN and the left dorsolateral prefrontal cortex were anti-correlated in healthy control adults but positively correlated in the ADHD group (Hoekzema et al., 2013). The fourth study (E. B. Liddle et al., 2011) found an attenuated deactivation of the DMN in children suffering from ADHD during an inhibitory control task which has been associated with increased task difficulty. Taken together, several studies have found that the anti-correlation between the DMN and the CCN is attenuated during both resting state (Castellanos et al., 2008; Sun et al., 2012) and task state (Fassbender et al., 2009; E. B. Liddle et al., 2011) in children, adolescents or adults with ADHD.

While FNC alterations thus seems to play an important role in ADHD and appear similar across different states, most functional connectivity studies so far focused on alterations in either resting or task state. A core aim of the current neuroimaging research is to better understand

differences between resting and task states and how these relate to behavior. Exploring the state-dependent interactions (interaction between resting and task state) of FNC with clinical scores or behavioral performance will allow further insights about the link between FNC and behavior patients with psychiatric disorders such as children with ADHD. Here we used fMRI recordings during resting state, and in a response inhibition task with consistently altered neural processing in ADHD (Hart et al 2014) in 16 children with ADHD and a matched healthy control group (16 children) obtained within a single session. The main question we addressed is how FNC differs during the resting state and during a response inhibition task in healthy control children and children with ADHD, and how these state and group effects interact. For more specific inhibition-related FNC alterations, we focused on the subcomponents of the DMN and their interaction with inhibition relevant brain regions of the CCN such as ACC, SMA and IFG. We calculated a high order ICA (independent component analysis) over both states and groups to reveal functional relevant components and analyzed how clinical severity scores modulate FNC connectivity.

We hypothesized that in both states, children with ADHD show impaired FNC between components of the DMN and CCN in the form of an attenuated anti-correlation between the networks in children with ADHD. Furthermore, we expected correlations between the anti-correlation and clinical ADHD scores.

3.3 Methods

3.3.1 Participants

Thirty-two children aged 9 to 12 years participated in this study and were matched for age, gender and were included in the analyses (Table 1). The 16 individuals with ADHD were recruited from our outpatient clinic and the 16 healthy controls from local schools. Patients with ADHD had to fulfill criteria for combined type based on ICD-10 (F90.0) (World Health Organization, 2012) and DSM-IV-TR (314.01) ("Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)," 2013). All participants underwent the German version of semi-structured clinical interview (K-SADS-PL) (Kaufman et al., 1997) to investigate their phenotype including psychiatric comorbidities. Furthermore, the parents rated the behavior of their children with the Conners Parent Rating Scale (Conners et al., 1998) and we collected measures of the Child Behavior Checklist (CBCL) (Achenbach and Edelbrock, 1983). Groups were matched for age, sex, IQ and handedness (Oldfield, 1971). Further details can be obtained from Table 1. Exclusion criteria for all subjects were IQ < 70 on the abbreviated Wechsler Intelligence Scale for Children (Waldmann, 2008), other psychiatric disorders than the typical comorbidities, neurological disorders, or pre- and/or post-natal complications. Patients had to discontinue medication for at least 48 h prior to testing. An additional six ADHD subjects from the original sample of n = 22 ADHD and n = 16

control children had to be excluded from further fMRI analysis, four due to excessive movements >3mm and two for not completing both tasks. The study was approved by the local ethics committee and met the guidelines of the declaration of Helsinki. All participants, as well as the children's parents, gave written informed consent prior to the investigation. Subjects received a voucher for their participation.

Table 1: Demographic and clinical data

Measure	Controls (n =16) Mean ± SD	ADHD (n =16) Mean ± SD	Statistics p value
Age (years)	10.44 ± 1.09	10.5 ± 1.09	*t (30) = 0.87, p > 0.05*
Sex (m/f)	11 / 5	12 / 4	χ^2 (2) = 1.55, p > 0.05
Handedness (l/r)[1]	0 / 16	1 / 15	χ^2 (2) = 1.03, p > 0.05
IQ estimate [2]	118.56 ± 10.00	117.81 ± 10.26	*t (30) = -0.21, p > 0.05*
Conners index (parent rating)[3]	53.00 ± 8.94	68.93 ± 8.87	*t (30) = 4.82, p < 0.001*
Sum score inattention	49.64 ± 9.76	66.87 ± 9.33	*t (30) = 4.86, p < 0.001*

Sum score hyperactivity	48.29 ± 9.56	67.80 ± 9.64	*t (30) = 5.47, p < 0.001*
Medication	0	14	

Note: [1] According to Oldfield (1971); [2] IQ was estimated based on the WISC subtests, which were conducted.IQ estimate was calculated using model 56 by Waldmann (2008); [3] Derived from a research version of the Conners-3.

3.3.2 Tasks

3.3.2.1 Stop-Signal Task

A Stop-Signal task with an event-related design was used measuring the ability to withhold a dominant response (Go) (Rubia et al., 2003). An already triggered and possibly initiated response to a pre-potent Go stimulus needs to be inhibited after a Stop signal follows unexpectedly the Go signal after a few hundreds of milliseconds. The whole task lasted 6 min. Prior to scanning, written and oral instruction, followed by a short training consisting of 20 trials was given to the subjects. The stimuli were presented using Presentation® software (Neurobehavioral Systems, Version 13.1.05.30.09). Further details about the task are described in Rubia and colleagues (Rubia et al., 2003).

3.3.2.2 Resting State

The 8 min resting state sessions consisted of alternating eyes open (eo) and eyes closed (ec) blocks of 2min duration each starting with eyes open (i.e. eo-ec-eo-ec). In the eyes open blocks a fixation star was presented on the screen. The resting state networks appear robust with respect to different conditions such as the presence or absence of visual inputs (eyes closed vs eyes open), low-level task (fixation cross) or eye movement (Fox et al., 2005). The instruction to close or open the eyes after each block was given by an audio-visual stimulus. The stimuli were presented using Presentation® software (Neurobehavioral Systems, Version 13.1.05.30.09).

3.3.3 fMRI acquisition and analyses

3.3.3.1 Recordings

Simultaneous EEG-fMRI was recorded using a 3T Philips Achieva whole-body system (Philips Medical Systems, Best, the Netherlands) with a 32-elements receive head coil (Philips SENSE Head coil 32-elements) specifically designed for simultaneous recordings of EEG and fMRI. First we recorded phase and magnitude images at different echo times (TE_1 = 4.3 ms, TE_2 = 7.3 ms), which were used to generate a voxel displacement map. An echo planar imaging (EPI) sequence was applied for fMRI data recordings [TR: 1960ms, TE: 30ms, 35

slices, 3 x 3 x 3mm voxel size, 0.7 mm slice gap, FA: 80°, FOV: 240 x 240 x 129mm]. Slices were aligned to AC-PC line. After acquisition of functional images, T1-weigthed images were recorded with a 3D MP-RAGE sequence [FOV: 270 x 254 x 176mm, sagittal orientation, 1 x 1 x 1 mm voxel size, TR: 6.9ms, TE: 3.2ms, flip angle: 9°].

3.3.3.2 fMRI Analyses

Preprocessing and analyses were conducted using SPM8 (Wellcome Trust Centre for NeuroImaging, UCL, London, UK). Images were realigned and unwarped using field maps to correct for motion artifacts, susceptibility artifacts and motion-by-susceptibility interactions (Andersson et al., 2001; Hutton, 2002) and slice time corrected. Next, T1-weighted anatomical images were segmented using the SPM8 procedure "New Segment" and the Forward Deformations obtained from the segmentation were applied to the anatomy and the realigned and co-registered EPI files. Finally, spatial smoothing (6x6x6 mm^3) was applied. The images had an isotropic resampled resolution of 2x2x2 mm^3.

3.3.4 Group ICA analysis

A single-group spatial ICA was run across all subjects and sessions (stop task and resting state) using GIFT toolbox (Calhoun et al., 2001).

Rest and task data were analyzed in one group ICA to get a tighter comparison between the two states (Arbabshirani et al., 2013). First, single-subject datasets were compressed using principal component analysis (PCA: 120 components), then the reduced data from all subjects and sessions were concatenated and a PCA on the whole group was performed. Second, spatial ICA was applied using the infomax algorithm (Bell and Sejnowski, 1995) with subsequent back reconstruction into single subjects and sessions (Calhoun et al., 2001; Erhardt et al., 2011) to obtain 100 independent components. These 100 independent components resulted in 100 spatial component maps (SM) and associated time courses (TC) for each subject and session. To ensure the stability of the group ICA, we repeated the ICA algorithm 100 times using ICASSO (Himberg et al., 2004). Components with a quality (iQ: the difference between intra-cluster and extra-cluster similarity) below 0.9 were excluded from further analysis.

3.3.5 Components selection

One sample t-tests were conducted for each SM to obtain regions peak activation clusters and mean power spectra of each TC was computed (E. Allen et al., 2011). First, all of the components were visually inspected and artifactual ones were excluded. Known visual artifacts in independent components are vascular, susceptibility, ventricular and edge regions corresponding activation clusters. Additionally, we

checked the mean power spectra of each component and ensured that selected components showed higher low frequency spectral power. Further, we did a spatial correlation with the gray matter, white matter and CSF template maps of the SPM 8 toolbox to be sure that the main peak activation cluster of the selected components fell on gray matter. These steps of artifact detection procedure resulted in 57 selected components out of the 100 independent components obtained. In a next step, the selected components were spatially correlated with spatial network templates of known intrinsic connectivity networks (E. Allen et al., 2012). These correlations resulted in three different intrinsic networks: default mode network (DMN: 12 components), cognitive control network (CCN: 16 components) and somatomotor network (SMN: 9 components). 20 components were assigned to other networks (sub-cortical, visual, cerebellar, auditory) and were not used for further analysis. The components of the CCN and SMN were further assigned to components (each 2 ICs) that are involved in the response inhibition neural process: ACC, SMA and right IFG.

3.3.6 Functional network connectivity (FNC)

We used the Mancovan toolbox (E. Allen et al., 2011) to determine the FNC between and within the networks. We used diagnosis (ADHD vs. healthy control) and state (resting state vs task state) as covariates. Subjects-specific TCs were detrended, despiked and filtered using a

fifth-order Butterworth low-pass filter with a high frequency cut-off of 0.15Hz. We used a general high-cut off filter of 0.15Hz as it was shown that FNC results of rest and task states are not significantly dependent on specific filtering choice (Arbabshirani et al., 2013). The TCs of each component were used to calculate FNC (Jafri et al., 2008) as pairwise correlation of the average connectivity during the scan durations. The correlation values were z-scores transformed using Fischer's transformation. We used only the first 6min of the resting state data with two eyes open blocks and one eyes closed block to have the same duration as in the Stop task.

3.3.7 FNC statistic

We calculated for each group (ADHD and healthy control) and each state (resting state and task state) a correlation matrix for the three networks DMN and CCN (including ACC, SMA and right IFG). Finally, to determine the significant group differences of ADHD vs healthy control in the resting state and the task state, paired t-tests were conducted on the two groups. The difference between the two groups and the states was calculated with a paired t-test of the contrasts ADHD (task vs. rest) and healthy control (task vs. rest). The cut-off P-values for all tests was set at $p < 0.01$ without correction for multiple comparisons.

3.3.8 Correlations wit clinical scores

To examine possible associations between the FNC of the fMRI results and the clinical scores we used the FNC correlation values (Pearson r) between the DMN-CCN connectivity and correlated them with the clinical scores of the CBCL and Conners parents' questionnaires. The significance level was set at $p < 0.05$.

Table 2: Task performance variables				**Statistics**
Measure	Group	Mean	SD	t-Values (df = 30)
Accuracy Go [% correct]	ADHD	92.19	9.17	*t = -0.843*
	Control	94.35	4.63	*P = 0.408*
Accuracy Stop [% correct]	ADHD	55	7.13	*t = 1.108*
	Control	52.81	3.4	*P = 0.280*
Mean reaction time Go [ms]	ADHD	522.99	66.83	*t = 0.710*
	Control	503.96	83.72	*P = 0.483*

Mean reaction time Stop unsuccessful [ms]	ADHD	472.02	51.55	*t = 0.351*
	Control	462.7	92.86	*P = 0.729*
Mean Stop-Signal delay [ms]	ADHD	363.81	86.39	*t = -0.042*
	Control	365.16	95.31	*P = 0.967*
Stop-Signal reaction time (SSRT) [ms]	ADHD	159.17	87.31	*t = 0.803*
	Control	138.8	51.56	*P = 0.430*

3.4 Results

3.4.1 Behavioral results

Accuracy, number of errors, mean reaction time, stop-signal delay and stop-signal reaction time (SSRT) did not differ between the groups (Table 2).

3.4.2 Group ICA analyses

The component selection is described in the methods part. Out of the 57 non-artifactual ICs we used the 12 ICs of the DMN and 4 ICs of the CCN/SMN for further analysis. Figure 1 and Table 3 shows the relevant ICs for each network and the corresponding peak activation clusters. The DMN networks are grouped into more anterior and more posterior components.

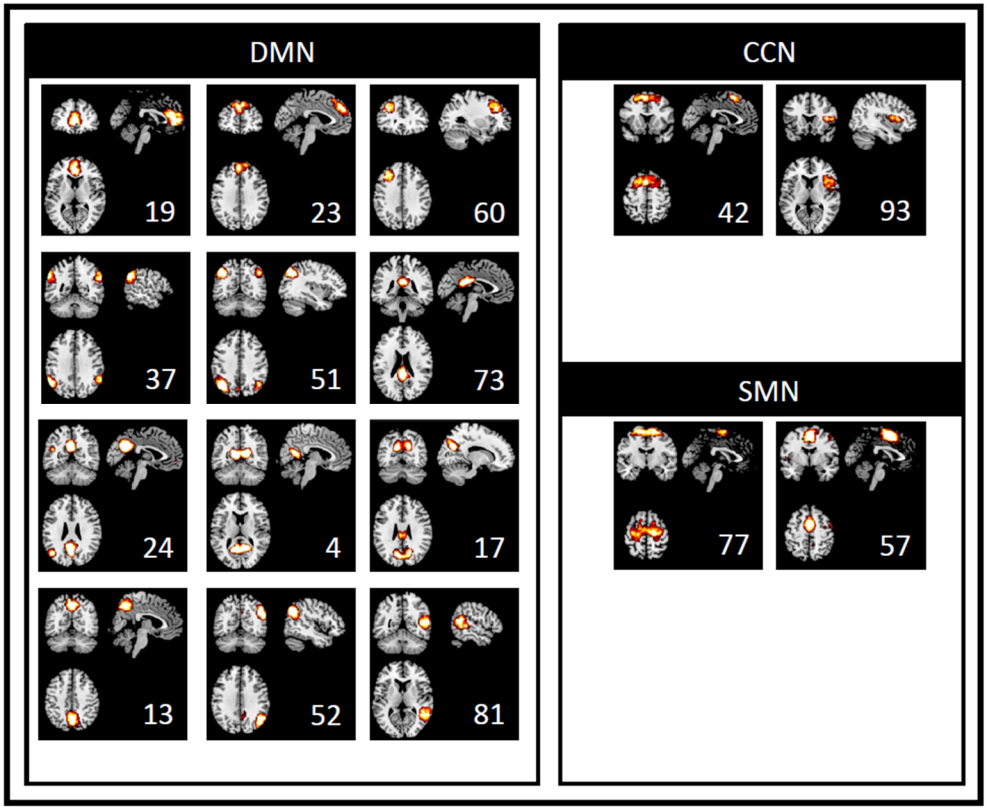


Figure 1: Spatial maps of the (artefact free) independent components (IC) and its peak activations sorted into the three networks default mode (DMN), cognitive control (CCN) and somatomotor (SMN). Component labels and peak coordinates are provided in Table 3.

Table 3: fMRI peak activations of the ICs

Region	BA	Cluster size (CC) left/right	Talairach coordinates left/right x	y	z	t_{max} score left/right
DEFAULT MODE NETWORKS IC 19 (0.97)						
L/R Anterior Cingulate	10, 24, 25, 32, 33	8.3/8.2	-2/4	43/35	5/7	23.3/24.0
L/R Medial Frontal Gyrus	9, 10	9.6/7.9	-2/4	42/52	15/1	20.0/18.9
L/R Superior Frontal Gyrus	6, 8, 9, 10	3.5/3.2	-8/8	54/56	-1/-1	16.3/14.3
L/R Cingulate Gyrus	23, 24, 32	2.3/2.0	-2/2	29/32	28/26	10.3/10.5

IC 23 (0.98)						
L/R Superior Frontal Gyrus	6, 8, 9, 10	16.3/14.5	-4/8	48/50	33/32	22.5/19.6
L/R Medial Frontal Gyrus	6, 8, 9, 10	10.5/9.9	-4/6	44/50	33/36	21.2/21.4
L/R Middle Frontal Gyrus	8, 9, 10, 47	1.9/3.1	-22/40	54/16	19/42	9.7/7.1
IC 60 (0.97)						
L Middle Frontal Gyrus	6, 8, 9, 10, 46	17.8	-28	27	26	22.8
L Superior Frontal Gyrus	6, 8, 9, 10	13	-26	35	30	19.4
L Precentral Gyrus	6, 9	0.9	-32	23	34	19.3
L Medial Frontal Gyrus	6, 8, 9, 32	3.4	-22	36	26	17.0
L Anterior Cingulate	24, 25, 32	2	-20	30	21	16.6
L Cingulate Gyrus	24, 31, 32	2.8	-16	25	36	11.6
IC 37 (0.96)						

L/R Supramarginal Gyrus	40	5.4/5.2	-55/55	-53/-43	32/30	20.8/17.5
L/R Inferior Parietal Lobule	7, 39, 40	8.0/9.7	-53/55	-52/-47	39/41	18.8/15.3
L/R Superior Temporal Gyrus	13, 21, 22, 39, 42	4.3/4.5	-53/59	-55/-55	29-27	18.6/11.4
L/R Angular Gyrus	39	2.1/1.2	-48/51	-55/-56	36/36	17.1/10.1
IC 51 (0.97)						
L/R Inferior Parietal Lobule	7, 39, 40	8.7/5.4	-38/40	-66/60	44/38	20.8/13.6
L/R Superior Parietal Lobule	7	3.0/1.5	-34/38	-68/-66	44/46	20.3/11.9
L/R Precuneus	7, 19, 39	7.7/2.9	-34/34	-64/-66	42/42	19.5/11.0
L/R Angular Gyrus	39	2.5/1.8	-34/40	-60/-56	36/36	16.4/12.0
IC 73 (0.93)						
L/R Posterior Cingulate	23, 29, 30, 31	3.3/3.3	-2/8	-34/-34	22/22	26.1/26.1
L/R Cingulate Gyrus	23, 24,	7.7/6.5	-2/4	-34/-34	26/26	23.7/23.9

	31, 32					
IC 24 (0.97)						
L/R Precuneus	7, 19, 23, 31, 39	11.1/5.4	-8/2	-51/-61	30/33	21.6/19.0
L/R Cingulate Gyrus	23, 24, 31, 32	4.4/2.9	-4/2	-53/-61	27/29	20.7/19.6
L/R Cuneus	7, 18, 19	0.5/0.4	-2/2	-64/-64	31/31	19.6/18.0
L/R Posterior Cingulate	23, 29, 30, 31	3.8/1.9	-4/4	-53/-57	23/25	18.7/16.1
L Middle Temporal Gyrus	19, 21, 22, 37, 39	5.2/1.6	-42	-61	27	19.0
L Angular Gyrus	39	2.2/1.1	-44	-63	31	18.4
L Superior Temporal Gyrus	22, 39	3.2/1.6	-46	-59	27	16.7
IC 4 (0.98)						

L/R Posterior Cingulate	23, 29, 30, 31	5.4/6.3	-12/16	-54/-52	12/14	36.2/35.3
L/R Precuneus	7, 19, 23, 31, 39	4.2/3.2	-10/16	-59/-57	18/23	31.1/24.8
L/R Parahippocampal Gyrus	19, 27, 28, 30, 34, 35, 36, 37	5.7/5.1	-12/12	-48/-46	4/4	28.0/23.8
IC 17 (0.97)						
L/R Cuneus	7, 18, 19	2.2/1.7	-10/10	-66/-68	33/33	30.9/27.8
L/R Precuneus	7, 19, 23, 31	11.6/13.4	-12/12	-65/-64	29/33	29.2/28.8
L/R Cingulate Gyrus	23, 24, 31	3.7/3.8	-6/6	-24/-18	27/27	17.7/16.8
L/R Posterior Cingulate	23, 29, 30, 31	1.8/1.9	-6/6	-34/-40	24/20	14.2/14.3

IC 13 (0.98)						
L/R Precuneus	7, 19, 23, 31	18.0/17.1	0/6	-54/-54	45/47	26.1/25.9
L/R Cingulate Gyrus	24, 31	1.4/2.0	-4/4	-45/-49	39/39	13.7/18.7
L/R Superior Parietal Lobule	7	2.8/3.1	-6/10	-65/-65	55/55	16.7/14.7
IC 52 (0.96)						
R Angular Gyrus	39	0.8/2.2	46	-57	30	20.0
R Middle Temporal Gyrus	19, 21, 22, 39	0.2/5.4	50	-61	29	19.0
R Superior Temporal Gyrus	13, 22, 38, 39	0.3/4.7	50	-57	29	18.7
R Inferior Parietal Lobule	7, 39, 40	0.4/6.5	48	-62	38	18.5
R Supramarginal Gyrus	40	0.0/4.9	50	-57	32	18.5
R Precuneus	7, 19, 31,	0.6/7.0	42	-70	37	17.4

	39					
R Superior Parietal Lobule	7	0.0/1.0	36	-70	44	12.8
IC 81 (0.91)						
R Middle Temporal Gyrus	19, 21, 22, 37, 39	0.3/13.6	46	-44	6	22.3
R Superior Temporal Gyrus	13, 21, 22, 38, 39, 41, 42	0.6/16.2	48	-48	10	22.3
R Inferior Parietal Lobule	40	0.3/4.0	50	-42	24	15.7
R Supramarginal Gyrus	40	0.0/3.2	50	-49	23	15.1
COGNITIVE CONTROL NETWORKS IC 42 (0.97)						
L/R Superior Frontal Gyrus	6, 8	12.5/12.5	-6/12	16/10	53/53	21.8/18.6
L/R Medial Frontal Gyrus	6, 8, 32	5.8/5.1	-10/12	18/22	47/47	17.9/18.6

L/R Middle Frontal Gyrus	6, 8, 9, 10	10.4/9.5	-16/24	11/20	60/47	16.4/14.2
IC 93 (0.91)						
R Insula	13	3.2/8.4	38	12	9	19.70
R Inferior Frontal Gyrus	9, 10, 13, 44, 45, 46, 47	0.6/13.9	36	22	8	18.30
R Precentral Gyrus	6, 43, 44	1.0/4.7	42	16	7	18.10
SOMATOMOTOR NETWORKS IC 77 (0.96)						
L/R Middle Frontal Gyrus	6	3.4/2.6	-20/14	-14/-12	60/61	21.6/27.2
L/R Superior Frontal Gyrus	6, 8	5.3/5.3	-18/14	-14/-14	63/65	23.6/24.8
L/R Medial Frontal Gyrus	6	4.9/5.7	-10/10	-11/-13	61/60	21.6/24.4

IC 57 (0.95)						
L/R Medial Frontal Gyrus	6, 8, 32	5.8/6.8	-4/4	3/1	53/55	16.3/18.8
L/R Cingulate Gyrus	24, 31, 32	7.2/7.9	0/8	4/6	46/40	16.4/18.4
L/R Superior Frontal Gyrus	6, 8, 9	2.8/4.7	0/2	6/5	49/55	15.3/17.0

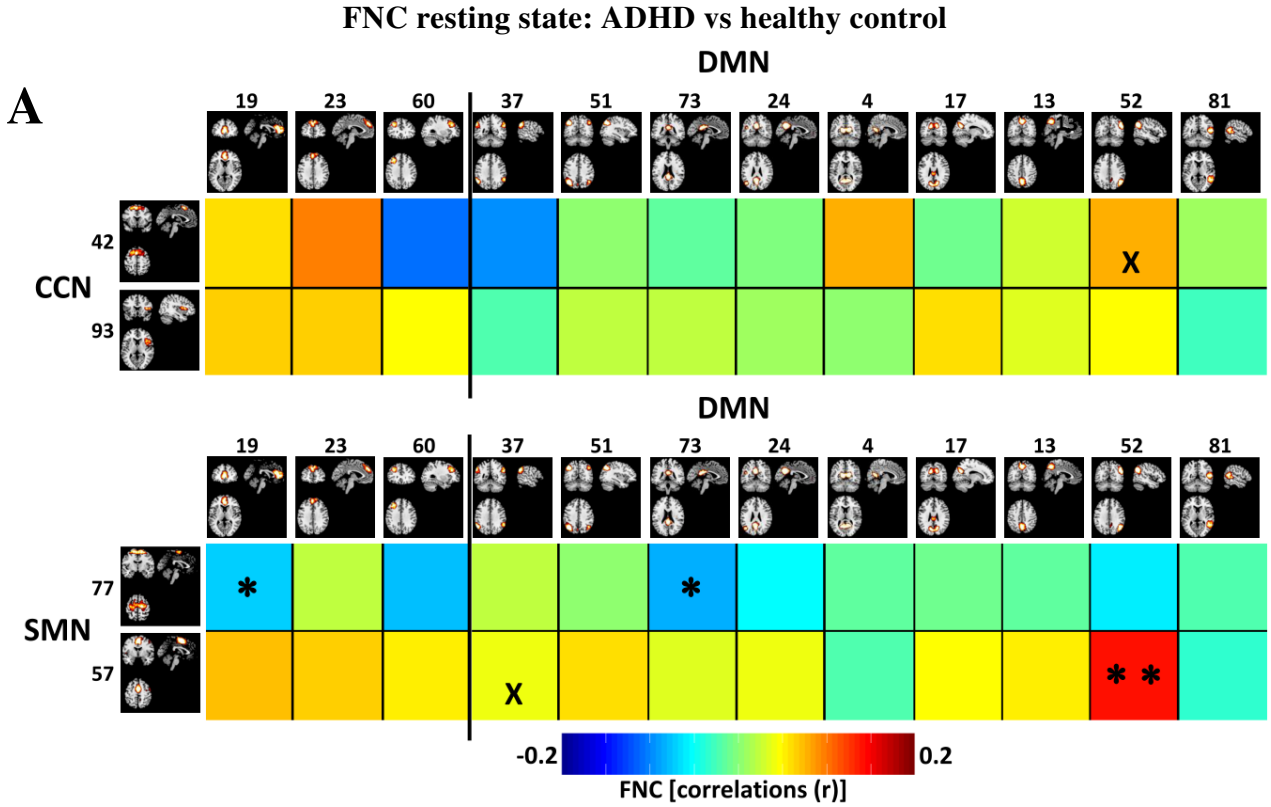
3.4.3 FNC

3.4.3.1 Resting state

Significant group differences between ADHD and control children were found for the components of the DMN and the SMN (cf. Fig. 2A): anterior regions of the DMN (IC 19: ACC, medial and superior frontal gyrus), as well as posterior regions of the DMN (IC 73: posterior cingulate and cingulate gyrus) showed a higher anti-correlation with regions of the SMN (IC 77: middle, superior and medial frontal gyrus) in children with ADHD. In contrast, right lateralized posterior regions of the DMN (IC 52: right angular, middle temporal and superior temporal gyrus, right inferior parietal lobule and right precuneus) showed a higher anti-correlation with regions of the SMN (IC 57: medial frontal, superior frontal and cingulate gyrus) in the control children.

Two FNC pairs showed a significant positive correlation with the Conners parents ADHD index reflecting symptom severity (cf. Fig. 2A & 2B): (1) The FNC pair of the posterior DMN (IC 52: right angular, middle temporal and superior temporal gyrus, right inferior parietal lobule and right precuneus) and CCN (IC 42: superior, medial and middle frontal gyrus) ($r = 0.448$; $p = 0.015$; cf. Fig. 2B, left), (2) as well as the FNC pair of the posterior DMN (IC 37: supramarginal gyrus, inferior parietal lobule, superior temporal and angular gyrus) and SMN (IC 57: medial frontal, superior frontal and cingulate gyrus) ($r = 0.371$; $p = 0.047$; cf. 2B, right) correlated positively with the ADHD

index. In other words, the higher the ADHD index, the lower the anti-correlation in these FNC pairs.


FNC resting state: ADHD vs healthy control
A
DMN
19
23
60
37
51
73
24
4
17
13
52
81
42
CCN
93
X
DMN
19
23
60
37
51
73
24
4
17
13
52
81
77
SMN
57
*
*
X
* *
-0.2
0.2
FNC [correlations (r)]

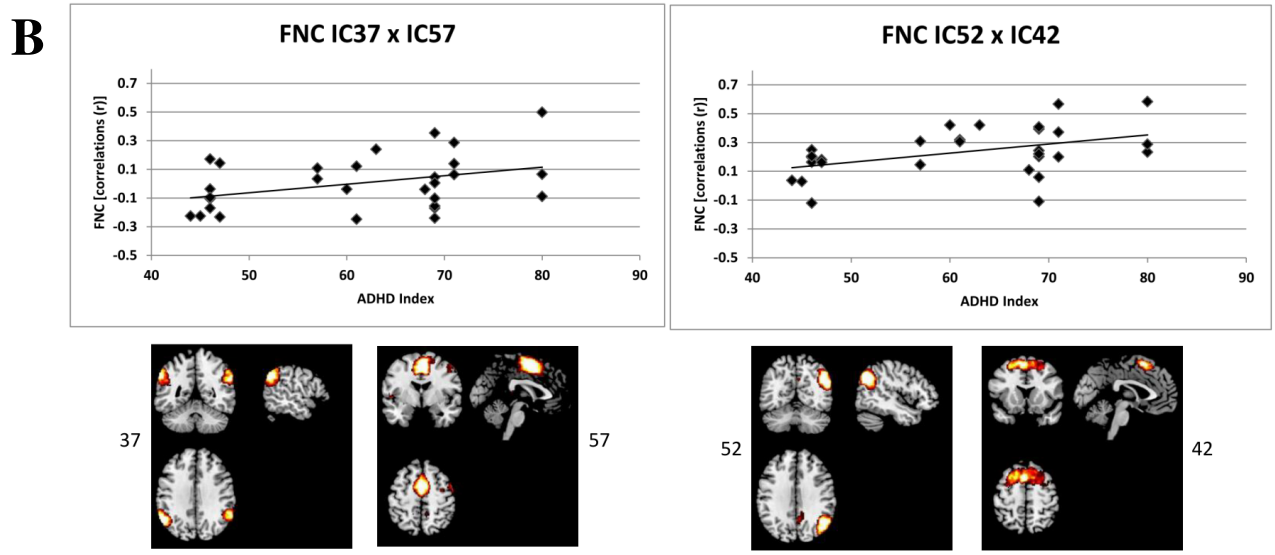
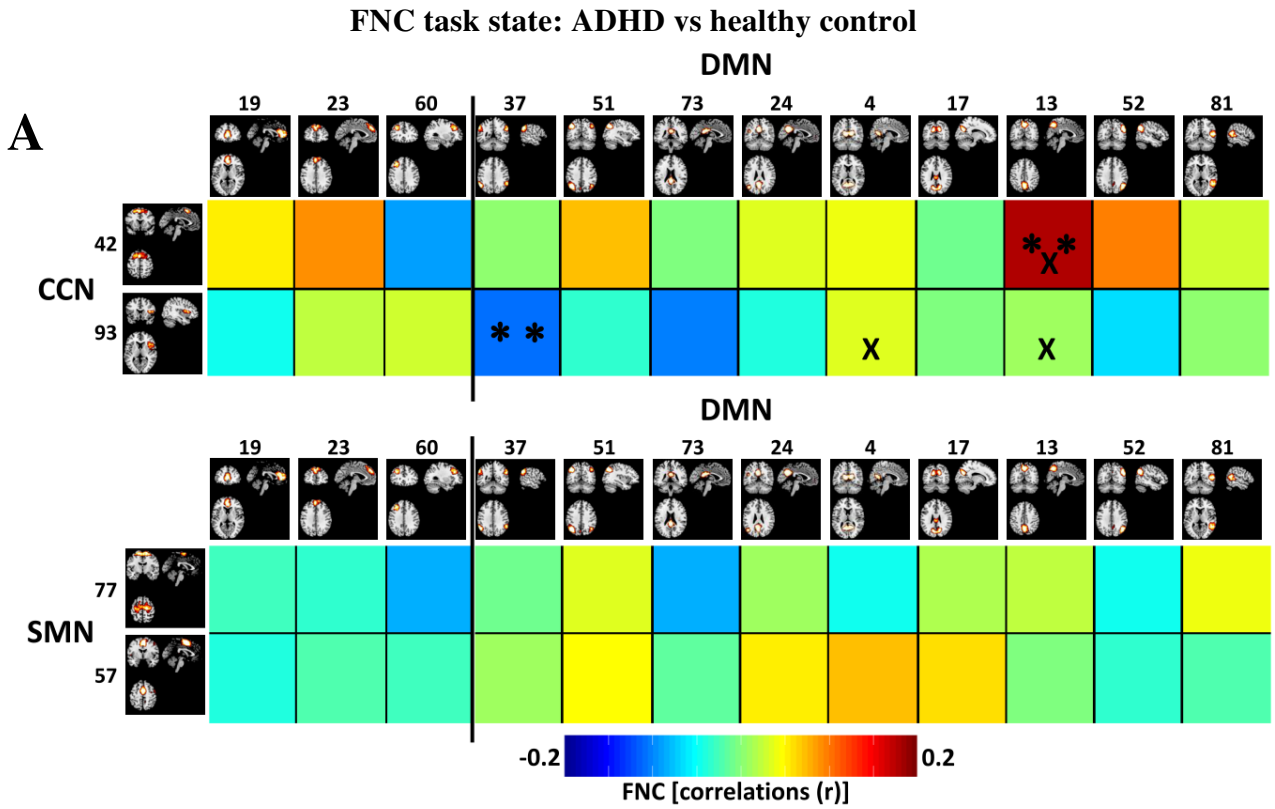


Figure 2: **A:** Functional network connectivity (FNC) correlation matrix differences between children with ADHD and a healthy control group (ADHD vs. healthy) of ICs during resting state. Thick black line partitions frontal and posterior parts of the DMN. Blue indicates higher anti-correlation in children with ADHD; red indicates higher anti-correlation in healthy control group. Stars: FNC pairs surviving the t-test (∗ = $p<0.05$; ∗∗ = $p<0.015$). X: FNC pairs show a significant correlation with the Conners ADHD index (see Figure 1B). **B:** Correlation between FNC pair and Conners ADHD index with corresponding IC maps. Results are reported using $p<0.05$.

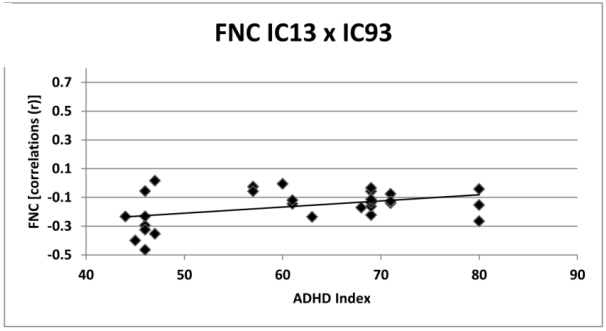
3.4.3.2 Task state

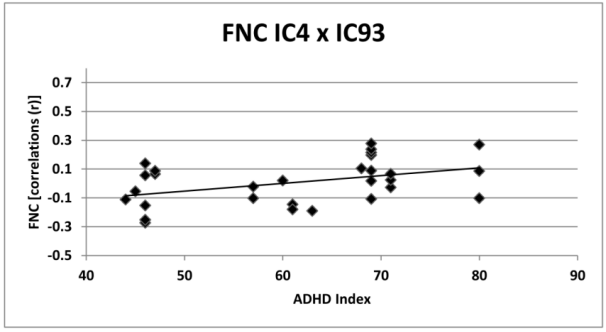
Significant differences between ADHD and control children were only found between components of the DMN and the CCN (cf. Fig. 3A): Posterior regions of the DMN (IC 13: precuneus, cingulate gyrus and superior parietal lobule) and regions of the CCN (IC 42: superior, medial and middle frontal gyrus) showed a higher anti-correlation in the control children. Whereas posterior regions of the DMN (IC 37: supramarginal gyrus, inferior parietal lobule, superior temporal and angular gyrus) showed a higher anti-correlation with right lateralized regions of the CCN (IC 93: right insula and right inferior frontal gyrus) in children with ADHD.

Three FNC pairs showed a significant positive correlation with the Conners parents ADHD index (cf. Fig 3B): The posterior DMN (IC 13: precuneus, cingulate gyrus and superior parietal lobule) and (1) CCN (IC 42: superior, medial and middle frontal gyrus) ($r = 0.507$; $p = 0.005$) pair, as well as the posterior DMN and (2) CCN (IC 93: right insula and right inferior frontal gyrus) ($r = 0.415$; $p = 0.025$) pair correlated positively with the ADHD index (Fig. 3B, left). A third positive correlation with the ADHD index was found in the FNC pair of the posterior DMN (IC 4: posterior cingulate and precuneus) and CCN (IC 93: right insula and right inferior frontal gyrus) ($r = 0.420$; $p = 0.023$; Fig 3B, right). Similar to the resting state results, the anti-correlation of these FNC increased with the ADHD index.

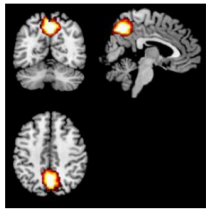

FNC task state: ADHD vs healthy control
A
DMN
19
23
60
37
51
73
24
4
17
13
52
81
42
CCN
93
DMN
77
SMN
57
-0.2
0.2
FNC [correlations (r)]

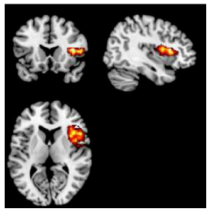
B


FNC IC13 x IC93
FNC [correlations (r)]
0.7
0.5
0.3
0.1
-0.1
-0.3
-0.5
40
50
60
70
80
90
ADHD Index


FNC IC4 x IC93
FNC [correlations (r)]
0.7
0.5
0.3
0.1
-0.1
-0.3
-0.5
40
50
60
70
80
90
ADHD Index

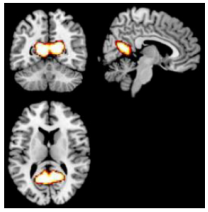
13

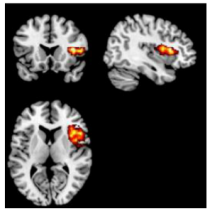




93

4





93

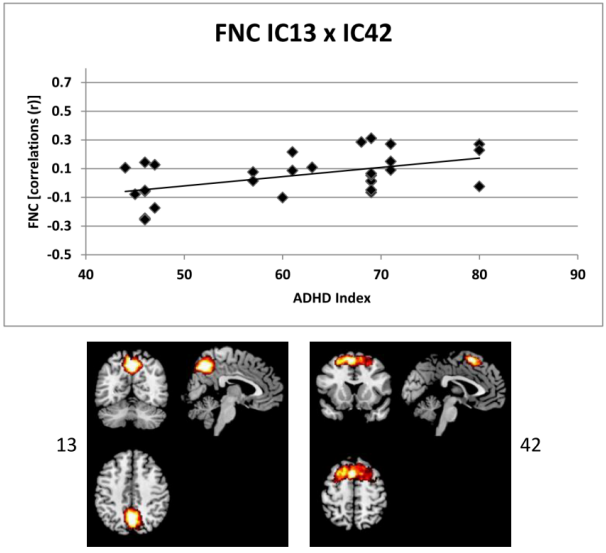


Figure 3: A: Functional network connectivity (FNC) correlation matrix differences between children with ADHD and a healthy control group (ADHD vs. healthy) of ICs during task state. Thick black line partitions frontal and posterior part of the DMN. Blue indicates higher anti-correlation in children with ADHD; red indicates higher anti-correlation in healthy control group. Stars: FNC pairs surviving the t-test (* = $p<0.05$; ** = $p<0.015$). X: FNC pairs show a significant correlation with the Conners ADHD index (see Figure 1B). **B:** Correlation between FNC pair and Conners ADHD index with corresponding IC maps. Results are reported using $p<0.05$.

3.5 Discussion

In this paper we studied the state dependency of FNC alteration in children with ADHD across the resting state and a stop-signal task. We focused on FNC between subcomponents of the DMN and brain regions, which are involved in the executive process of inhibition (CCN, SMN). During resting state FNC showed significant group differences between anterior and posterior parts of the DMN and regions related to the SMN. In the task state, FNC only revealed significant group differences in long-range connections of the posterior part of the DMN and the CCN. Furthermore, the clinical ADHD scores (Conners index) correlated with this FNC, reflecting decreasing anti-correlation with increasing ADHD scores. Taken together, these findings support the evidence that state-dependent FNC disruption in anti-correlated networks between the DMN and task-positive networks such as CCN or SMN is a central feature in ADHD (Bush, 2009; Castellanos and Proal, 2012; Cortese et al., 2012; Konrad and Eickhoff, 2010). Moreover, this study highlights the importance of functional connectivity across different cognitive states to reveal a more holistic view of a psychiatric disease.

3.5.1 Resting state FNC

In the resting state we found three significant FNC pairs between subcomponents of the DMN and the SMN (Figure 2A). Two of them showed a higher anti-correlation in children with ADHD while one revealed a higher anti-correlation in the healthy control group. Both FNC pairs with higher anti-correlation in children with ADHD included correlations between anterior or posterior components of the DMN (IC 19: ACC, medial and superior frontal gyrus; IC 73: posterior cingulate and cingulate gyrus) with the same component of the SMN (IC 77: middle, superior and medial frontal gyrus). IC 77 of the SMN includes the premotor cortex (PMC) and the supplementary motor area (SMA). Those regions have an important impact on cognitive motor control (Nachev et al., 2008) and may be involved during the resting state as the participants were advised to lie as still as possible. Alterations of motor control in ADHD are associated with subnormal activation in the prefrontal motor control system (Bush, 2009; Mennes et al., 2011; Rubia et al., 1999). Our findings of a higher anti-correlation between the DMN and the PMC/SMA show such an altered FNC of motor control, and may reflect that inhibiting motor activity requires additional cognitive control during the resting state in ADHD. In contrast, FNC between right lateralized posterior regions of the DMN (IC 52: right angular, middle temporal and superior temporal gyrus, right inferior parietal lobule and right precuneus) and SMN (IC 57: medial frontal, superior frontal and cingulate gyrus) showed a higher anti-

correlation in the control group. These results are consistent with the findings of Castellanos (Castellanos et al., 2008) and Sripada (Sripada et al., 2014) and colleagues. Compared to the IC 77, the IC 57 of the SMN is more anterior and includes besides the SMA also parts of the anterior cingulate cortex (ACC). The ACC belongs to the anterior attention system and is well known to be altered in ADHD (Bush, 2009; Castellanos et al., 2008), and children with ADHD have consistently decreased connectivity (less anti-correlation) between the posterior DMN and brain regions belonging to the anterior attention system. This could be explained by children with ADHD not meeting the attention required for in order to "stay" in a resting state. Our resting state analysis lasts six minutes and children are instructed to lie still and to fixate a cross in the center of the screen during the eyes open intervals. These instructions may have induced additional cognitive control processes such as attentional and motor control. Interestingly, the peak activation clusters of the two components IC 77 and IC 57 partly overlap, but show opposite group differences regarding anti-correlation. This shows how important the parcellation of functional networks into subcomponents is. Taken together, these three FNC differences suggest that children with ADHD need additional motor control processes to compensate for impaired attentional control processes over DMN in the resting state. Moreover, these results suggest that resting state is more like a task than a real resting state situation for children with ADHD.

The correlations between FNC and clinical ADHD scores revealed further (Figure 2B) that children with a higher ADHD score have a lower FNC anti-correlation between subcomponents of the DMN and CCN or SMN. The IC of the DMN include brain regions of the bilateral supramarginal, angular and superior temporal gyrus and the inferior temporal lobule, whereas the counterpart the CCN and SMN comprise the PMC, SMA, ACC and frontal eye fields (FEF). Both these FNC pairs reflect long-range connections between posterior part of the DMN and anterior part of the CCN/SMN. Several studies could show that the long-range connections are altered in children with ADHD (Castellanos et al., 2008; Fair et al., 2010). Our correlation results suggest that reduced anticorrelation of long-range connections between the posterior DMN and the anterior CCN/SMN also reflect the severity of ADHD symptoms. As these long-range connections undergo prominent maturation (Fair et al., 2008), their alterations in ADHD could reflect a maturational delay (Posner et al., 2014)..

3.5.2 Task state FNC

The task state revealed group differences in two FNC pairs between posterior subcomponents of the DMN and the CCN (Figure 3A). FNC between the DMN and components of the CCN was reduced for one CCN component (IC 42) and increased for another CCN component (IC 93) in the ADHD group compared to controls. The control group

showed higher anti-correlation between long-range FNC pairs of the posterior part of the cingulate cortex/precuneus of the DMN (IC 13) and the PMC/SMA/FEF of the CCN (IC 42). In the resting state we had found similar results between the DMN and the IC 57. Compared to the IC 57 of the SMN the IC 42 of the CCN has its peak activation more frontal and does not include the parts of the ACC. This result support the hypothesis of a reduced anti-correlation between long-range connection in ADHD (Castellanos et al., 2008) also for inhibitory task states. The second significant task FNC alteration links the posterior DMN (IC 37: bilateral supramarginal, angular and superior temporal gyrus and the inferior temporal lobule) and the right lateralized subcomponent of the CCN (IC 93: right insula and IFG) but instead reflects a higher anti-correlation in the ADHD group. These opposite FNC alterations in ADHD might be explained by differences in the location and function of the involved DMN subcomponents. While the IC 37 is more lateralized and revealed a higher anti-correlation with the right IFG, the subcomponents of the DMN surrounding the central PCC/precuneus showed a higher anti-correlation FNC in the control group (Figure 4A/B). Its interaction with the right IFG might be important as it could explain the higher anti-correlation in children with ADHD as an alteration in FNC between the posterior attention system (IC 37) and the executive process of inhibition (IC93). The failure of DMN attenuation during a task presumably leads to more errors in response inhibition (Eichele et al., 2008; Li et al., 2007).

These results suggest that subcomponents of the DMN have different interactions with task-positive networks (Elton and Gao, 2015). More lateralized subcomponents of the DMN had different FNC than more central ones like the PCC or precuneus. This is in line with Sripada and colleagues (Sripada et al., 2014), who reported prominent lateralization of FNC in ADHD, and with recent results that the DMN may also be used for task relevant processing (Piccoli et al., 2015; Vatansever et al., 2015). Additionally, there is also evidence that the right IFG and (pre-) SMA are key regions of the response inhibition system, but their function seems to be task- and subject specific (Mostofsky and Simmonds, 2008).

Similar to the resting state, the correlation between the task FNC pairs and the clinical scores of the Conners ADHD index indicate decreasing anti-correlation with increasing severity (Figure 3B). Interestingly, all subcomponents of the DMN include the PCC (IC 93). It shows the importance of the posterior cingulate cortex/precuneus within the DMN in ADHD and also other psychiatric disorders (Broyd et al., 2009; Castellanos et al., 2008; Greicius, 2008; Leech and Sharp, 2013; Sonuga-Barke and Castellanos, 2007b; Utevsky et al., 2014). These correlations further support the hypothesis that children with ADHD fail to attenuate connections between core regions of the DMN such as the precuneus and task relevant regions during cognitive tasks.

3.5.3 State dependent FNC

This study addressed the state dependency of FNC alterations in ADHD through direct comparison of two different states in the same subjects and session. Altered FNC anti-correlations were found in both states but mainly concerned state-specific networks: In the resting state the interaction of the DMN was only detected with the SMN and in the task state with the CCN. These results indicate that the FNC alterations in children with ADHD are state-dependent. Moreover, our results illustrated that especially subcomponents of the DMN show state-dependent interactions with task-specific components. Interestingly, we found in both states FNC pairs that showed higher anti-correlation in children with ADHD. This might be explained by the parcellation of the DMN in several subcomponents, because the FNC with posterior lateral subcomponents of the DMN revealed opposing group differences compared to centered subcomponents regard the anti-correlation. An interpretation of this distinction is speculative however as the specific function of these anti-correlations needs further investigations.

The higher anti-correlation in the healthy control group and its positive correlation with the ADHD score add to growing evidence that the attenuation of the DMN is state-independent as we found these outcomes in both states. Additionally, the disruption of FNC between long-range correlations with the PCC/precuneus was found in both states, which supports this aspect. Taken together, even though, the reduced DMN attenuation and some other ADHD-related findings held

across states , these results illustrate that the subcomponents of the networks and their FNC are highly state-dependent, whereas the DMN attenuation is a general finding across both cognitive states.

3.5.4 Limitations

Our aim was to study a group of ADHD children meeting criteria for combined subtype and an equally sized, well-matched healthy control group within a narrow age range to reduce within group developmental effects. Given the strict inclusion criteria, the resulting relatively small number of subjects in each group is the main limitation of this study. As a consequence the p-values could not be corrected for multiple comparisons. In addition, the interpretation of anti-correlated FNC is not fully clear, even though several studies already discussed potential implications and its contribution to ADHD. Additionally, we parcellated the DMN into several subcomponents. On the one hand, this approach allows for more fine-grained and detailed spatial analyses but on the other hand the interpretation of the FNC between subcomponents of the DMN and regions of the CCN/SMN are difficult to compare with previous FNC results between the full DMN and CCN/SMN networks.

3.6 Conclusion

In this study we investigated the FNC of different states in children with ADHD and a healthy control group. Comparing the two states, we could show that the FNC between subcomponents of the DMN and CCN/SMN showed state specific differences between the two groups. During resting state FNC showed significant group differences in pairs between anterior and posterior parts of the DMN and regions related to the SMN. In contrast, the task state FNC differences between children with ADHD and the control group were restricted to long-range connections of the posterior part of the DMN and the CCN. In both states we showed that higher anti-correlations between the DMN and CCN/SMN in children with ADHD might represent the disruption of state-dependent processes such as motor control in resting state and attentional alertness in task state. Interestingly, we found in both states FNC pairs that showed lower as well as higher anti-correlation in children with ADHD. This could be explained by the parcellation of the DMN and emphasizes the importance of specific subcomponents in functional networks. Furthermore, the correlation between clinical ADHD scores revealed reduced FNC anti-correlation with increasing symptom severity in children with ADHD. This study highlights the importance of functional connectivity across different cognitive states to reveal a more holistic view of a psychiatric disease. Furthermore, the results emphasize the benefit of considering functional networks subcomponents.

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Conflict of interest

The other authors declare no potential conflicts of interest.

4 General discussion

This dissertation project aimed to understand state-dependent cognitive processing at rest and during task in health and in patients with ADHD. A cognitive state may be described as an arousal/ vigilance level, which could be driven or is dependent on the timing (e.g. reaction time: measured as the speed of cognitive processing by reaction time). There is a relationship between the timing and task-relevant networks (Konrad et al., 2006) suggesting that the individual timing could have an influence on brain networks/ activations and vice versa. Hence, we suggest that the timing plays an important role in regulating different cognitive states and might be an important factor to regulate and influence transitions of different states. Here, we focused especially on this transition from one state to another and how this transition is affected in psychiatric diseases such as ADHD. Additionally, we investigated the individual timing in two cognitive tasks (response inhibitions tasks) and its influence on brain activations. It is poorly understood, how individual differences and diseases affect transitions from one specific brain state to another. The two studies conducted in this thesis, investigated the temporal variability in healthy individual subjects (Study A) and the functional connectivity of different arousal states in children with ADHD (Study B). These results contribute to a better understanding of how different states shape cognitive processing in health and disease. Subsequently, the results of these studies will be summarized and discussed.

4.1 Study A

Executive functions and cognitive control such as response inhibition are important brain states that are required in daily situations. Inhibition allows humans to withhold unwanted behaviors, what is optimal and important for a goal-directed behavior. The timing of the neural inhibition process, which may be linked to regions and tasks but also individual differences in behavior, seems to be a critical aspect of such goal-directed behavior. In this study, we used simultaneous EEG-fMRI to investigate the timing and spatial activation patterns of common and task-specific brain mechanisms related to response inhibition. Our results identified a common inhibition network across tasks within the right IFG. The temporal resolution of the EEG provided further insights into the neural correlates of task specific interindividual variability of inhibitory timing. Our results showed that ERP latency differences of the Stop P300 across subgroups of individuals correspond to different fMRI activations in the anterior cingulate cortex and the left IFG.

These findings emphasize that the task state in such inhibition tasks consists not only one state. Multiple dynamic and partly task specific sequences balance between processes reflecting readiness, action and inhibition. The timing of these states and transitions between the processes is particularly critical in inhibition tasks. Furthermore, this timing shows particularly prominent individual differences in the Stop

tasks having a distinct neurophysiological (P300 latency) and hemodynamic signature. Hence, the inhibition process is not just reflecting several different processes supporting brain functions such as attention, working memory and response selection (Chambers et al., 2009), but the timing and interaction of these different processes is critical. A different timing (reaction time) resulted in in different neurophysiological measures (P300 latency) and distinct BOLD activation patterns. This leads to the conclusion that the human behavior is dependent on a complex interplay of neuronal processes and timing, which finally leads to individual differences in brain mechanisms and goal-directed behaviors. Individual differences in cognitive activity could be used for subgroup classification and the interpretation of neuronal disorders such as attention deficit hyperactivity disorder (ADHD) (Aron et al., 2003; Rubia et al., 2001; 1999; van Rooij et al., 2015). Especially group classification in heterogeneous disorders such as ADHD (Nigg et al., Sonuga-Barke, 2002) may be used to detect interindividual activation differences. Similar to the task state - that is composed of a highly dynamic, multistate system – the resting state is a dynamic system organized of temporally correlated activity of spatially segregated brain structures.

The link between the task- and resting state requires an adaption and modulation of different networks by external and internal stimuli. These dynamic modulations are of increasing importance in clinical and translational medicine (Sporns, 2011). Failures of brain networks across cognitive states seem to have an important impact on psychiatric

disorders such as ADHD, which are discussed in study B.

4.2 Study B

Evidence showed that ADHD reflect dysfunctions in several specific regions that subserve cognitive, motor and attentional functions (Bush, 2009), but recent models shift their focus from regional brain abnormalities to dysfunction in network organization. Posner et al. (Posner et al., 2013) showed that children with ADHD have deviations in two different neural systems including executive attention and emotional regulation, which emphasizes the importance to explore multiple neural networks. The most prominent (resting state) network associated with ADHD is the DMN (Castellanos et al., 2008; Fair et al., 2010; Sun et al., 2012; Uddin et al., 2008). It has even been suggested that ADHD could be considered a DMN disorder (Sonuga-Barke and Castellanos, 2007b). The transition from rest to a task state and the deactivation or suppression of the DMN is associated with momentary lapses in attention (Weissman et al., 2006). Several studies suggest that a defective transition from rest to a task state, and malfunctions of the deactivation or suppression of the DMN can lead to failures in meeting attentional demands (Posner et al., 2014). We studied the state dependency of FNC (functional network connectivity) alteration in children with ADHD across resting state and task state (stop-signal task). We focused on FNC between subcomponents of the DMN and brain regions, which are involved in the executive process of inhibition (CCN:

cognitive control network; SMN: somatomotor network). As mentioned, several studies investigated the DMN and its association with ADHD (Castellanos et al., 2008; Fair et al., 2010; Sun et al., 2012; Uddin et al., 2008). We parcelated the DMN into subcomponents to have more refined view on the DMN function and to investigated how anterior and posterior subcomponents of the DMN differ in their interaction with the task-positive networks involved in the executive process of inhibition. This approach is supported by our results depicting that two partly overlapping components of the DMN showed opposing FNC with task-positive networks. During resting state, FNC showed significant group differences (children with ADHD vs healthy control group) between anterior and posterior parts of the DMN and regions related to the SMN. In the task state, FNC only revealed significant group differences in long-range connections of the posterior part of the DMN and the CCN. These findings support the evidence that state-dependent FNC disruption between the DMN and task-positive networks such as CCN or SMN is a central feature in ADHD (Bush, 2009; Castellanos and Proal, 2012; Cortese et al., 2012; Konrad and Eickhoff, 2010). Interestingly, we found in both states FNC pairs that showed higher anti-correlation in children with ADHD, which was not expected (Castellanos et al., 2008). This might be explained by the parcellation of the DMN, because the FNC with posterior lateral subcomponents of the DMN revealed opposing group differences compared to centered subcomponents regarding the anti-correlation. This shows how important the parcellation of functional networks into sub-

components is and illustrates that especially subcomponents of the DMN show state- dependent interactions with task-specific components. Taken together, failures of brain networks across cognitive states seem to have an important impact on psychiatric disorders such as ADHD. This study highlights the importance of functional connectivity across different cognitive states to reveal a more holistic view of a psychiatric disease. The link between different states seems to require an adaption of different networks. These dynamic modulations will become of increasing importance in clinical and translational medicine (Sporns, 2011).

4.3 Limitations

The main limitation of both studies is the low number of subjects leading to low statistical power. In study A the group split allows only 12 respective 10 subjects per group. These low numbers might be the main reason that few results remained significant after proper correction for multiple comparisons. In study B, we correlated the time course of multiple brain regions with each other to reveal the difference between two groups for each of the functional correlations. For a proper statistical comparison, we should do a correction for the multiple correlations here. However, the small number of subjects did not allow for such a correction. We are aware of this limitation and we tried to include a proper statistical analysis. Unfortunately, we were not able to include a correction for multiple comparisons, but the statistical

level was strengthened including a tightened threshold of the p-value (e.g. study A: $p<0.0005$). Future studies should include more subjects or combine the imaging data with data from other studies to increase the number of subjects and thereby the statistical power.

Another limitation of study A was the design of the two response inhibitions tasks. A key problem in the design of the contrasts between the two tasks is the fact that the NoGo flanker task includes a response-conflict element with congruent and incongruent trials including an active conflict monitoring process, which will not be present in the Stop task. We were aware about this conflict between the two tasks. However, we wanted to compare two widely used and compared response inhibition tasks in recent literature in the same subject and session. The novel contribution of study A is the (temporal) design of the tasks, measuring both tasks within the same session (within 20 minutes) in the same subject. Hence, this strict (temporal) design avoids potential learning and mood effects and might allow a better comparison of the two tasks. However, future studies comparing two tasks with the same neuronal process should be aware of such a conflicting design and correct for it. This could be done by removing or adding such a conflict monitoring process in one task or by controlling it via an adaptive design of the contrast (e.g. adding a separate regressor for the conflict).

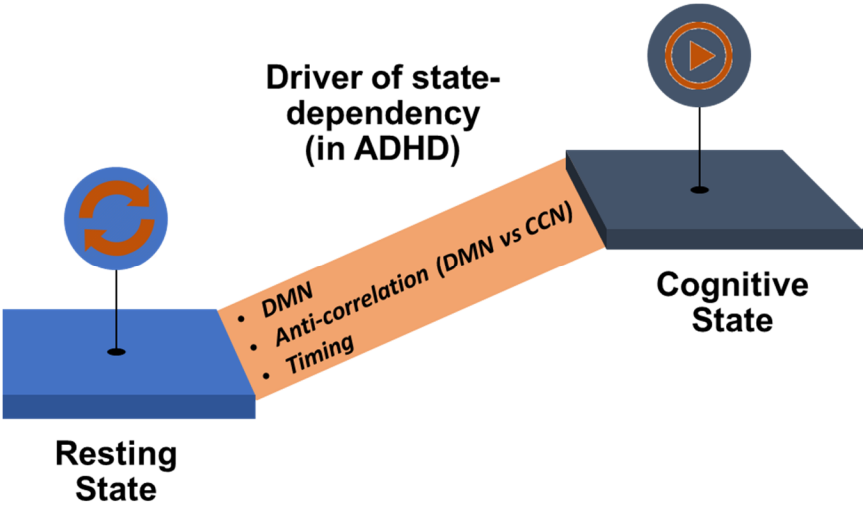
4.4 Conclusion

In the introduction of this thesis we tried to illustrate the complex dynamics interaction of the cognitive states using an analogy: 'The resting state behaves like an "active standby" mode that is prepared and ready to "switch" to the task mode to adapt the changing environments'. The resting state has significant functional and behavioral impact on the task state (Northoff et al., 2010). This raises the question if the distinct components of human cognitive ability are based on the relationship of different cognitive states, and our ability to switch between them. To address this question, network dynamics needs to be examined in finer detail by combining high spatial resolution fMRI with high temporal resolution EEG data (Hampshire and Sharp, 2015). Hence, we investigated two studies while using simultaneous EEG-fMRI measurements to further understand how different cognitive states and their transition behave in health and disease. Study A focused on the individual timing adding the temporal aspect to the cognitive system of response inhibition. Here, we investigated how the individual timing can influence the cognitive state and vice versa. These findings emphasized that the task state is a dynamic and time-dependent process that is essential for higher cognitive performance. The interplay of neuronal processes and its timing is another important aspect, which needs to be consider if we want to understand the highly dynamic system of the brain. In study B, we compared different cognitive states in health and disease (ADHD) showing that failures of brain networks in each of the cognitive states could have an important im-

pact on psychiatric disorders such as ADHD. Simply put, malfunctions in a cognitive network of one state could have major consequences for another state and may result in a pathophysiology of neuropsychiatric disorders. The interplay can progress in either of two directions of the two cognitive states (resting- and task state). The resting state activity can interact with the stimulus-induced task state, thus impacting behavioral and/or mental states. Conversely, the task activity can influence the resting state functional networks and modulate this basal level of activity (Northoff et al., 2010). Taken together, cognition and its underlying mechanisms are dependent on a timely synchronized interaction of several functional networks across different cognitive (vigilance) states. Minor inconsistencies in this complex system might lead to neuropsychiatric disorders.

We mentioned in the introduction that scientific approaches recently began to disentangle the brains function as a dynamic system, where cortical regions, cell assemblies or even single neurons interact with each other. This thesis adds another piece of this puzzle to understand the brains mechanisms, which needs to be completed on all neuronal levels. For instance, it is not fully understood how changes in anatomy facilitate the functional relationships in the brain. The structural and functional systems of the brain are modeled in different complex networks (Bullmore and Sporns, 2009). It is important to link neuroimaging studies with fMRI or EEG at the systems level with findings from research methods that describe physiological mechanisms that drive

these network changes. Hence, for a full understanding of the brains cognitive function, we need to identify the cellular changes and molecular mechanisms that underlie these functional networks. Maybe a reasonable next step is to follow up promising results with large enough samples and better designs. In the limitations, we discussed that the sample size in our studies is critical and that a larger cohort may reveal additional more refined and statistically better results. Especially, study A, including subgroups and individual measures (timing) would profit of a larger sample. Additionally, a more aligned and coordinated task design (e.g. task order) of both studies might lead to clearer results when comparing different tasks or states. Consequently, the overall goal would be to understand the system as whole and determine how it is be related to (neuropsychiatric) diseases.



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7 Curriculum Vitae

Anthony Schläpfer

Address:	Haselstrasse 18 CH-8335 Hittnau Switzerland
Date and Place of birth:	25th March 1985, Davos
Nationality:	Swiss
Phone:	+41 79 338 07 76
Email:	anthonyschlaepfer@gmail.com

Education

07/2017	**Ph.D. in Neuroscience**, University of Zurich: *„Resting states of the brain and state dependent information processing in health and disease: Linking resting state and task regulation in development and ADHD"*
07/2017	**ZNZ International PhD program in Neuroscience**, ETH Zurich and University of Zurich
06/2012	**Master of Science in Biology**, Neurosciences, University of Zurich: "*Neuroanatomical correlates of economic preferences"*

05/2011	**Bachelor of Science in Biology**, University of Zurich
2001 to 2006	**Swiss Matura** Sportgymnasium Davos (economic orientation)

Practical Experience

since 03/2017	**Senior Consultant,** Executive Insight Healthcare Consultants, Zürich
08/2015 to 02/2017	Consultant**,** Executive Insight Healthcare Consultants, Zürich
05/2013	Teaching assistant, undergraduate courses Biology, University of Zurich (BIO406 Experimental Human Studies)
03/2013 to 07/2015	Supervision of Master students (Biology and Psychology of ETH and University of Zurich)
10/2012 to 07/2015	Execution and supervision of simultaneous EEG/fMRI recordings
06/2012 to 07/2015	Research assistant, University Clinics for Child and Adolescent Psychiatry (UCCAP), University of Zurich
05/2010 to 09/2010	Internship in Neuroeconomics, Laboratory for Social and Neural System Research (SNS Lab, Prof. Dr. Ruff), University of Zurich
06/2007 to 10/2011	Assistant as an electrical fitter, Suter und Bähler Installationen AG in Zurich

Conferences

10/2014	Resting States and State Dependent Information Processing in Health and Disease, Monte Verita, Ascona; Co-Organizer, talk and poster presentation
09/2014	Conference on Resting State/Brain Connectivity, Massachusetts Institute of Technology (MIT), Boston; poster presentation
06/2014	Annual meeting of the Organization for Human Brain Mapping (OHBM), Hamburg; poster presentation
05/2014	Computational Psychiatry Meeting, Zurich; poster presentation
09/2013	International conference on Basic and Clinical multimodal Imaging (BaCI), Geneva; poster presentation
10/2012	Deutsches EEG/EP Mapping Meeting (DMM), Giessen; talk

Computer Skills

Windows / Mac OSX	excellent
Word	excellent
PowerPoint / Keynote	excellent
Excel	good
Matlab	good

SPSS	good

Activities / Interests

1989 to 2012	Ice-Hockey goalie (HC Davos, HC Lugano, EHC Chur, EHC Frauenfeld, Swiss National Team Juniors)
currently	Fitness, Hiking, Reading, Cooking

Language Skills

German	mother tongue
English	fluent
French	conversant
Italian	basic knowledge